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TERESA GÓRNISIEWICZ

Labor induction at advanced maternal age

Indukcja porodu u pacjentek w zaawansowanym wieku

Praca doktorska

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Miejsce wykonania pracy:
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Pragnę złożyć najszczersze podziękowania
Panu prof. dr. hab. Hubertowi Hurasowi,
promotorowi niniejszej pracy doktorskiej,
za poświęcony czas oraz cenne rady,
a także za wsparcie i wyrozumiałość.

Nigdy nie zliczę trosk,
jakie w me wychowanie włożyliście,
Rodzice Kochani.
Dlatego dziś, na Drogiej Mamy ręce,
składam swój doktorat w podzięce.
Szkoda, Tato, że nie doczekałeś chwili
mojego osiągnięcia naukowego,
bo tak bardzo dopingowałeś mnie do tego.
Za wszystkie trudy i starania
dziękuję Tobie, Tato,
i moja Mamo Ukochana.

Spis treści

Publikacje zawarte w rozprawie doktorskiej

Niniejsza rozprawa doktorska powstała w oparciu o monotematyczny cykl trzech artykułów opublikowanych lub przyjętych do druku w czasopiśmie naukowym indeksowanym w bazie PubMed i znajdującym się na liście Journal Citation Reports (Thomson Reuters).

Trzy artykuły zawierają wyniki badania klinicznego dotyczącego poznania aspektów indukcji porodu u ciężarnych przeprowadzonego w Oddziale Klinicznym Położnictwa i Perinatologii Szpitala Uniwersyteckiego w Krakowie przy ulicy Kopernika 23.

Na rozprawę doktorską składają się następujące artykuły:

1. Gornisiewicz T, Kusmierska-Urban K, Huras H, Galas A. Comparison of Misoprostol versus Dinoprostone for delivery induction among pregnant women without concomitant disease. Ginekol Pol. 2020;91(12):726-732. doi: 10.5603/GP.2020.0119.
2. Gornisiewicz T, Huras H, Kusmierska-Urban K, Galas A. Pregnancy-related comorbidities and labor induction — the effectiveness and safety of dinoprostone compared to misoprostol. Ginekol Pol 2021;92(9):647-658. DOI: 10.5603/GP.a2021.0092 Pubmed: 34105752.
3. Gornisiewicz T, Kusmierska-Urban K, Huras H, Galas A. Factors associated with caesarean section in women referred for preinduction – a nested case-control study in dinoprostone and misoprostol groups. Ginekol Pol. DOI:10.5603/GP.a2021.0168 Online ahead of print.

Wprowadzenie

Najważniejszym celem indukcji porodu jest poprawa wyników okołoporodowych zarówno u noworodka, jak i u matki. Udana indukcja porodu jest rozważana w przypadku zakończenia porodu drogami natury w ciągu 24 godzin bez powikłań matczynych i noworodka z wysokim (≥ 8 punktów) wynikiem w skali Apgar. Znalezienie bezpiecznej, szybkiej i skutecznej metody indukcji porodu jest kluczowym elementem rosnącego zapotrzebowania na aktywną opiekę prenatalną, szczególnie że aż 30–40% kobiet rodzących drogami natury przechodzi procedurę indukcji porodu[1].

Decyzja o odpowiednim momencie zakończenia ciąży, która byłaby najlepsza zarówno dla dziecka, jak i dla matki, zawsze była i nadal bywa jeszcze kwestią dyskusyjną[2].
W dobie odraczania ciąży i rodzenia dziecka w zaawansowanym wieku kobiety, co ma uwarunkowania zarówno społeczne, jak i ekonomiczne, trzeba liczyć się z różnymi aspektami takich decyzji. Młode kobiety są zwykle zdrowe, ale u starszych kobiet w ciąży, zwłaszcza powyżej 40. roku życia, wzrasta ryzyko chorób współistniejących, takich jak nadciśnienie, cukrzyca czy otyłość[3].

Preindukcja i indukcja porodu – wskazania i przeciwwskazania

Wskazania i przeciwwskazania do przeprowadzenia procedury indukcji porodu są ogólnie znane; oszacowano już także pewną grupę czynników mających wpływ na jej skuteczność. Pośród wskazań matczynych można wymienić: nadciśnienie ciążowe, stan przedrzucawkowy, nadciśnienie przewlekłe, cukrzycę przedciążową i ciążową, cholestazę ciężarnych, przewlekłe schorzenia ciężarnej oporne na leczenie, konflikt serologiczny oraz wskazania płodowe: ciążę po terminie w 42. tygodniu ciąży, podejrzenie dużej masy płodu po 39. tygodniu ciąży, zakażenie wewnątrzmaciczne, hipotrofię płodu, nieprawidłowe wyniki badań, które mogą sugerować zagrażające niedotlenienie płodu (np.: nieprawidłowe KTG, graniczne wartości przepływów dopplerowskich w naczyniach płodowych), przedwczesne pęknięcie pęcherza płodowego po 37. tygodniu ciąży, wady rozwojowe płodu, obumarcie wewnątrzmaciczne donoszonego płodu w wywiadzie. Nowym wskazaniem stał się także sam wiek kobiety ciężarnej powyżej 40. roku życia do indukcji po 39. a przed 40. tygodniem ciąży[4].
Zarówno Polskie, jak i Kanadyjskie Towarzystwo Ginekologów i Położników pośród sytuacji klinicznych uniemożliwiających bezpieczny poród drogami natury i jednocześnie stanowiących przeciwwskazanie do indukcji porodu wymieniają: łożysko lub naczynia przodujące, nieprawidłowe położenie płodu (poprzeczne czy miednicowe), aktywne zakażenie narządów płciowych wirusem opryszczki zwykłej, nieprawidłową budowę miednicy, inwazyjnego raka szyjki macicy, a także dane z wywiadu: przebyte klasyczne cięcie cesarskie lub nacięcie macicy w kształcie odwróconej litery T, wyłuszczenie mięśniaków macicy oraz pęknięcie macicy[4, 5].

Preindukcja i indukcja porodu – metody

Zgodnie z powszechnie przyjętą definicją przez indukcję porodu rozumie się szereg czynności mających na celu zainicjowanie czynności skurczowej mięśnia macicy u ciężarnej kobiety przed jej pierwotnym rozpoczęciem i w efekcie urodzenie dziecka drogami natury[6].

W zdecydowanej większości przypadków decyzja o indukcji porodu z różnych przyczyn medycznych wiąże się jednak z niedojrzałością szyjki macicy do porodu, w związku z czym niezbędne staje się przeprowadzenie w pierwszej kolejności preindukcji porodu. Preindukcja porodu to szereg czynności mających na celu przyspieszenie dojrzewania szyjki macicy, jej skrócenie, rozwieranie i zmianę konsystencji[5]. Współczesna medycyna wypracowała zaledwie kilka narzędzi wpływających na stan szyjki macicy, które można ogólnie podzielić na metody mechaniczne i farmakologiczne. Spośród metod mechanicznych najczęściej stosowany jest cewnik Foleya, który wprowadzany jest w warunkach aseptycznych przez kanał szyjki macicy ponad ujście wewnętrzne, a wypełniony jest roztworem soli fizjologicznej. Metoda ta polega na mechanicznym drażnieniu ujścia wewnętrznego szyjki macicy, rozciąganiu dolnego odcinka macicy i pobudzaniu wydzielania endogennych prostaglandyn, które fizjologicznie doprowadzają do dojrzewania szyjki macicy. Cewnik Foleya można stosować także u kobiet po przebytym cięciu cesarskim.

Pośród metod farmakologicznych należy wymienić przede wszystkim prostaglandyny E1 i E2 oraz zdecydowanie rzadziej stosowane: mifepriston, glikokortykosteroidy, estrogeny, hialuronidazę, relaksynę oraz donory tlenku azotu. Prostaglandyna E2 – dinoproston jest od niedawna jedyną dopuszczoną już w Polsce substancją stosowaną do preindukcji farmakologicznej. Jest to naturalny czynnik produkowany przez doczesną i owodnię, który powoduje relaksację włókien kolagenowych szyjki macicy i wywołuje czynność skurczową samego mięśnia macicy[7]. Mizoprostol jest syntetycznym analogiem prostaglandyny E1 i wykazuje działanie na szyjkę macicy oraz indukcję porodu. Wykazano, że – w porównaniu z placebo – PGE1 podana dopochwowo jest skuteczniejszą metodą w uzyskaniu porodu drogami natury w ciągu 24 godzin, lecz zwiększa ryzyko hiperstymulacji macicy bez zaburzeń rytmu serca płodu[8]. W Polsce lek ten przez kilka lat posiadał rejestrację do preindukcji porodu ciąży żywej, wobec czego istnieje niewiele badań z zastosowaniem tego leku, szczególnie w grupie pacjentek powyżej 35. roku życia w populacji Polek.

Dożylna podaż oksytocyny jest natomiast obecnie najczęściej stosowaną metodą w indukcji porodu żywego płodu. Podawanie oksytocyny powinno być precyzyjne, najlepiej przy użyciu pompy infuzyjnej; zaleca się także ciągłe monitorowanie stanu płodu w trakcie wlewu. U ciężarnych po przebytym cięciu cesarskim, po przeanalizowaniu sytuacji położniczej, możliwe jest (ostrożne) stosowanie stymulacji porodu oksytocyną[9].

Wybór metody, zgodnie z zaleceniami Polskiego Towarzystwa Ginekologów i Położników, opiera się głównie na ocenie stanu położniczego u każdej pacjentki, preferencji decydującego lekarza, a najczęściej także na dostępności danej procedury w szpitalu. W obecnej praktyce żadna metoda przyspieszenia dojrzewania szyjki macicy nie wydaje się lepsza od innych, biorąc pod uwagę ich ogólną skuteczność i bezpieczeństwo. Oznacza to, że idealna metoda preindukcji porodu nadal jest poszukiwana, a pytanie, którą metodę wybrać, aby zmniejszyć ryzyko cięcia cesarskiego i poprawić wynik okołoporodowy, pozostaje otwarte.

Preindukcja i indukcja porodu – czynniki wpływające na skuteczność procedury

Indukcja porodu jako procedura medyczna może wiązać się z kilkoma powikłaniami, o których zawsze należy uprzedzić ciężarną; należy także uzyskać świadomą pisemną zgodę pacjentki na jej przeprowadzenie. Za niepowodzenie indukcji należy uznać brak jej skuteczności wymagający czasowego odroczenia oraz ponownego przeprowadzenia procedury lub konieczność zakończenia ciąży i porodu poprzez cięcie cesarskie, szczególnie w trybie pilnym – w przypadku zagrożenia stanu płodu lub pacjentki. Do takiej sytuacji może dojść m.in. przez pojawienie się hiperstymulacji mięśnia macicy z zaburzeniami rytmu serca płodu lub bez nich, wypadnięcie pępowiny, pęknięcie macicy, zapalenie błon płodowych, wyczerpanie sił pacjentki[5, 10].

W celu minimalizowania powyższych niekorzystnych sytuacji niezwykle istotne jest poznanie czynników warunkujących sukces procedury, a może jeszcze ważniejsze – wyodrębnienie czynników ryzyka niepowodzenia przeprowadzanej indukcji porodu. Bez wątpienia najistotniejsze znaczenie ma wspomniany stan szyjki macicy i jej dojrzałość. Do innych proponowanych czynników wpływających niekorzystnie na przebieg indukcji porodu i prowadzących do cięcia cesarskiego należą: wskaźnik masy ciała BMI > 40 kg/m^2, szacowana masa płodu powyżej 4000 g czy cukrzyca ciężarnej[11].

Inne badania, wśród czynników wpływających na przebieg porodu, wskazują: wiek kobiety, liczbę przebytych porodów lub zastosowanie znieczulenia zewnątrzoponowego i rodzaju metody indukcji porodu[12]. Lista ta jest z pewnością o wiele dłuższa, dlatego nadal prowadzone są badania nad ustaleniem, a co najważniejsze – nad wyodrębnieniem czynników modyfikowalnych, na które następnie można prewencyjnie zadziałać, dobierając odpowiedni rodzaj preindukcji i indukcji do danej ciężarnej.

Streszczenie pracy

Wstęp

Nowym wskazaniem do indukcji porodu stał się w ostatnim czasie wiek kobiety rodzącej, z uwagi na wykazaną rosnącą – wraz z wiekiem kobiety ciężarnej i czasem trwania ciąży – nie tylko liczbę powikłań matczynych, ale i płodowych, w tym liczbę nagłych zgonów wewnątrzmacicznych[13-16]. Nadal nieznane są przyczyny obserwowanych zależności. Część badaczy uważa, że w grupie kobiet 40-letnich za ciążę biologicznie dojrzałą można uznać 39. tydzień ciąży i należy wówczas rozważyć indukcję porodu w celu rozwiązania ciąży[17]. Wypracowanie najbezpieczniejszego i najkorzystniejszego sposobu indukcji porodu u pacjentek w zaawansowanym wieku, określonym jako 35. rok życia i więcej, jest zadaniem niezwykle ważnym i nadal otwartym. Zbyt mało przeprowadzono dotychczas badań dotyczących indukcji porodu u pacjentek w tej grupie wiekowej, co wiąże się z wieloma niewiadomymi dotyczącymi zarówno wyboru najlepszego postępowania, jak i czasu jego wdrożenia.

Cele

Cel główny:

Niniejsza praca doktorska miała na celu określenie, czy jedna z dwóch prostaglandyn – dinoproston lub mizoprostol – zastosowanych jako metody indukcji porodu u kobiet w zaawansowanym wieku, definiowanym powyżej 35. roku życia, przeważa nad drugą. W analizie brano pod uwagę skuteczność i bezpieczeństwo tych prostaglandyn.

Cele szczegółowe:

- ocena działania i porównanie dwóch metod farmakologicznej preindukcji porodu (dinoproston i mizoprostol) oraz opracowanie optymalnego sposobu łączenia tych metod,
- ocena, czy obecność choroby pacjentki w trakcie ciąży wpływa na skuteczność i bezpieczeństwo preindukcji dinoprostonem lub mizoprostolem,
- określenie czynników ryzyka cięcia cesarskiego przy zastosowaniu wyżej wymienionych prostaglandyn.

Skuteczność mierzona była czasem od wdrożenia leczenia do rozpoczęcia porodu i porodu, natomiast bezpieczeństwo mierzone było częstością cięć cesarskich w trybie

nagłym, obecnością komplikacji porodowych i niektórymi wskaźnikami zdrowotnymi u noworodków.

Materiał (dotyczy artykułów nr 1, 2 i 3)

Badaniem objęto 560 ciężarnych hospitalizowanych na Oddziale Położnictwa i Perinatologii Szpitala Uniwersyteckiego w Krakowie w okresie od stycznia 2015 r. do kwietnia 2019 r. Wszystkie artykuły oparte są o retrospektywną analizę kohorową, opracowaną na podstawie archiwalnej dokumentacji medycznej Szpitala.

Głównymi kryteriami włączenia pacjentek do poszczególnych analiz były: ciąża pojedyncza, położenie podłużne główkowe płodu, a także medyczne wskazanie do indukcji porodu. Innymi kryteriami włączenia były: wynik Bishopa $\leq$ 4 i brak aktywnego porodu przed podaniem leku.

Kryteria wykluczenia: pacjentki, u których określono oczekiwaną masę płodu powyżej 4500 g, łożysko przodujące, naczynia przodujące, wszelkie inne znane przeciwwskazania do porodu drogami natury lub wszelkie przeciwwskazania do stosowania prostaglandyn, takie jak przebyta operacja macicy lub cięcie cesarskie.

Oceniano m.in.: wiek matki, masę ciała kobiety przy przyjęciu, jej wzrost i wskaźnik masy ciała (*Body Mass Index* – BMI), liczbę ciąż, historię porodów, historię poronień, wiek ciążowy oraz szacunkową masę płodu wg pomiaru ultrasonograficznego, sposób rozwiązania, wskazania do cięcia cesarskiego, konieczność wyłyżeczkowania jamy macicy po porodzie drogami natury, nacięcie krocza, pęknięcie krocza, niedokrwistość wymagającą przetoczenia krwi, pojawienie się hiperstymulacji macicy, obecność lub brak *Streptococcus agalactiae* w pochwie i/lub odbycie, wymiary miednicy i obwód brzucha kobiet ciężarnych. Ponadto odnotowano płeć dziecka i wyniki dotyczące noworodka, w tym wynik w skali Apgar oraz masę urodzeniową i długość urodzeniową.

Do najczęściej odnotowywanych chorób współistniejących u ciężarnych należały: cukrzyca (ciążowa, przedciążowa), choroby nadciśnieniowe (przewlekłe, ciążowe), wewnątrzwątrobowa cholestaza ciężarnych, astma, małopłytkowość oraz niedoczynność tarczycy.

Metody (dotyczy artykułów nr 1, 2 i 3)

Preindukcję porodu przeprowadzono z użyciem żelu z dinoprostonem w dawce 0,5 mg (Prepidil, Pfizer Polska Sp. z o.o.) lub insertu dopochwowego z mizoprostolem w dawce 0,2 mg (Misodel, Ferring Pharmaceuticals Poland Sp. z o.o.). Przydział pacjentki

do podania danego preparatu zależał od preferencji lekarza kwalifikującego do procedury lub dostępności leku w danym momencie w Oddziale, bez możliwości retrospektywnego ustalenia specyficznych kryteriów wyboru.

Analizie poddano wskazania do indukcji porodu, czas od podania leku do porodu drogami natury lub czas do dowolnego porodu (pochwowego lub cesarskiego) oraz czas do rozpoczęcia porodu, jak również powikłania matczyne: nacięcie krocza, pęknięcie krocza, odklejenie lub zatrzymanie łożyska oraz niedokrwistość wymagającą transfuzji krwi i noworodkowe – punktację w skali Apgar.

W artykule nr 1 z badania zostały wyłączone wszystkie pacjentki z chorobami towarzyszącymi. W ten sposób uzyskane grupy stanowiły ciężarne z fizjologicznym przebiegiem ciąży, gdzie wskazaniem do indukcji porodu był wiek ciążowy. W uzyskanej w ten sposób grupie 240 pacjentek 93 ciężarne otrzymały mizoprostol, a 147 dinoproston, przy czym w tej drugiej podgrupie 39 kobiet otrzymało dodatkowo mizoprostol – z uwagi na brak reakcji po dinoprostonie.

W artykule nr 2 z całej grupy 560 ciężarnych do szczegółowej analizy wyłoniono grupę 320 kobiet z co najmniej jedną zdiagnozowaną chorobą, spośród których 117 otrzymało mizoprostol, a 203 dinoproston. W obu grupach wykazano odpowiednio 57 i 87 kobiet z niedoczynnością tarczycy, 27 i 28 z nadciśnieniem tętniczym, 23 i 65 z cukrzycą oraz 3 i 15 kobiet, które chorowały zarówno na cukrzycę, jak i na nadciśnienie, a 7 i 8 miało inne choroby. W grupie ciężarnych bez chorób dodatkowych mizoprostol otrzymały 93 pacjentki, a dinoproston – 147. W grupie dinoprostonu zidentyfikowano 100 kobiet, które dodatkowo otrzymały mizoprostol jako drugi lek. W każdej z grup wyodrębniono również kobiety powyżej i poniżej 35. roku życia.

W artykule nr 3 do badania zakwalifikowano całą grupę badawczą 560 ciężarnych. Wszystkie pacjentki podzielono według metody preindukcji, uzyskując grupę, która otrzymała dinoproston (grupa D; 250 osób) lub mizoprostol (grupa M; 210 osób), oraz trzecią grupę kobiet ciężarnych, która wymagała wprowadzenia drugiej prostaglandyny – najpierw dinoprostonu, a następnie mizoprostolu (grupa D + M; 100 osób), aby osiągnąć pożądany efekt.

W razie potrzeby wzmocnienia aktywności skurczowej macicy stosowano wlew z oksytocyną. Akcję serca płodu monitorowano przy pomocy zapisów kardiotokograficznych.

Analiza statystyczna

Analizę statystyczną prowadzono zgodnie z obowiązującymi wymogami dla badań naukowych w medycynie. W części przedstawiającej charakterystyki kobiet objętych badaniem – w zależności od charakteru przedstawianych cech (zmiennych) – charakterystyki opisowe przedstawiono, podając odsetki (dla cech skategoryzowanych) oraz średnie z odchyleniem standardowym i mediany z rozstępem międzykwartylowym (dla zmiennych ciągłych). Do określenia istotności statystycznej różnic pomiędzy grupami wykorzystano odpowiednio testy: chi-kwadrat lub – przy braku spełnienia założeń – test dokładny Fishera – dla zmiennych skategoryzowanych. W przypadku zmiennych ciągłych w pierwszym kroku weryfikowano zgodność z rozkładem normalnym za pomocą testu Shapiro-Wilka, a następnie i w zależności od spełnienia wymogu zgodności lub jego braku – odpowiednie testy t-Studenta lub U-Mann-Whitney'a. Na potrzeby artykułu nr 1, w celu określenia różnic w skuteczności pomiędzy lekami dinoproston a mizoprostol, biorąc pod uwagę prospektywny charakter obserwacji, zastosowano strategię analizy zgodnie z zaplanowanym leczeniem (*Intent to Treat*, ITT). Główne wyniki analizy oparto o model proporcjonalny regresji Coxa. Wykorzystanie tego modelu pozwoliło na określenie różnic pomiędzy badanymi lekami w skutecznym uzyskaniu porodu w czasie przy wyeliminowaniu potencjalnych dodatkowych czynników zakłócających, takich jak: przeszłość położnicza, wiek matki, stopień dojrzałości szyjki macicy w czasie podania leku czy zastosowanie oksytocyny. Uzyskany wynik ryzyka hazardu (HR) określa, na ile zastosowanie mizoprostolu zwiększa w czasie szansę skutecznego porodu.

Dodatkowo w artykule tym wykorzystano model analizy wariancji (ANOVA) z interakcją w celu odpowiedzi na pytanie, czy obserwowane pomiędzy różnymi lekami różnice w czasie trwania indukcji porodu zależą od wieku ciężarnych.

W artykule nr 2, podobnie jak w artykule nr 1, analizę prowadzono w grupach zgodnie ze strategią ITT. Do oceny obecności różnic w czasie trwania indukcji porodu oraz w występowaniu zdefiniowanych punktów końcowych – w zależności od zastosowanego leczenia lub obecności u ciężarnych chorób współistniejących – wykorzystano opisane powyżej techniki analizy. Dodatkowo, aby móc odpowiedzieć na pytanie, czy obserwowane różnice pomiędzy ciężarnymi bez chorób współistniejących w porównaniu do ciężarnych z chorobami współistniejącymi są inne u matek młodszych

niż 35 lat niż u matek w wieku 35 i więcej lat, wykorzystano statystykę Cochran-Mantel-Haenszel.

W artykule nr 3, którego celem było określenie czynników ryzyka cięcia cesarskiego w zależności od zastosowanej metody preindukcji, analizę przeprowadzono w schemacie zagnieżdżonego w obserwacji prospektywnej badania kliniczno-kontrolnego, w którym porównano ciężarne, które urodziły cięciem cesarskim, z ciężarnymi rodzącymi siłami natury. Do zidentyfikowania czynników ryzyka wykorzystano model regresji logistycznej. Model ten pozwolił na określenie niezależnych czynników ryzyka (po wyeliminowaniu istotnych czynników zakłócających), pokazując, o ile wzrastało (lub malało) ryzyko cięcia cesarskiego w sytuacji obecności określonej cechy u matki przy zastosowaniu dinoprostonu, mizoprostolu lub obu wymienionych leków.

Podsumowanie wyników

W niniejszym rozdziale krótko podsumowano dane zaprezentowane w artykułach 1–3.

Artykuł nr 1 opublikowany w „Ginekologii Polskiej"

Pierwszy artykuł skupia się na ocenie skuteczności w wywoływaniu czynności porodowej po zastosowaniu do preindukcji porodu dinoprostonu i mizoprostolu. W badaniu interwencja mizoprostolem zakończyła się porodem drogami natury w 68,8% przypadków w porównaniu z 76,9% w grupie dinoprostonu ($p = 0,207$). Wykazano, że stosowanie mizoprostolu istotnie skróciło zarówno czas do rozpoczęcia (9,9 vs 25,3 h, $p < 0,001$), jak i zakończenia porodu w porównaniu z zastosowanym żelem z dinoprostonem (niezależnie od ostatecznego sposobu rozwiązania – drogami natury lub cięciem cesarskim:14,5 vs 35,6 h, $p < 0,001$ oraz wyłącznie drogami natury: 15,1 vs 31,1; $p < 0,001$). Dodatkowo w modelu regresji Coxa wykazano, że mizoprostol zwiększył ponad dwukrotnie szansę rozpoczęcia porodu i porodu dziecka w porównaniu z dinoprostonem, także po uwzględnieniu zmiennych potencjalnie wpływających na wynik, takich jak: wiek kobiety, liczba ciąż, stan szyjki macicy czy zastosowanie oksytocyny. Istotnie więcej ciężarnych wymagało dodatkowej podaży oksytocyny do wzmocnienia czynności porodowej w grupie leczonej dinoprostonem (37,4%) w porównaniu do grupy z mizoprostolem (8,6%; $p < 0,001$).

Co ciekawe, szczegółowa analiza kategoryzująca badane kobiety według wieku nie powtórzyła uzyskanych dla całej grupy wyników. W badaniu wykazano, że wiek kobiety ciężarnej nie wpływa na efektywność stosowanych prostaglandyn: ani na rozpoczęcie porodu (czyli czas od zastosowania leku do początku pierwszego okresu porodu), ani do momentu urodzenia noworodka, jak również na czas trwania drugiego okresu porodu.

Przeanalizowano szczegółowo potencjalne niepożądane następstwa – zarówno dla matki, jak i dla płodu. Częstość cięć cesarskich oraz wskazania do wykonania zabiegu, a także powikłania matczyne nie różniły się istotnie między badanymi grupami. W grupie indukowanej mizoprostolem wykazano jedynie większą częstość zaburzeń rytmu serca płodu wymagających pilnego ciecia cesarskiego, choć bez istotności statystycznej. W analizie danych noworodkowych w grupie mizoprostolu zaobserwowano natomiast gorsze wyniki punktacji Apgar (9,4 vs 9,8; $p = 0,41$), niższe masy urodzeniowe (3385 g vs 3623 g; $p < 0,001$) i długości noworodków (54,9 cm vs 56 cm; $p = 0,008$), co

częściowo może wynikać ze statystycznie niższego wieku ciążowego pacjentek (39,7 vs 40,6; $p < 0,001$) w tej grupie w porównaniu do grupy z dinoprostonem.

W badaniu analiza czynników, które potencjalnie mogły wpłynąć na efekt każdej interwencji, nie wykazała różnic między grupami w zakresie wieku matki, liczby porodów, wcześniejszego porodu naturalnego, historii poronień, BMI pacjentki, punktacji w skali Bishopa przed podaniem leku lub szacowanej masy płodu.

Badanie wykazało, że stosowanie wkładki dopochwowej z mizoprostolem, w porównaniu z żelem z dinoprostonem, wydaje się zwiększyć szansę na poród i skracać czas do rozpoczęcia pierwszego etapu porodu oraz czas trwania porodu w całej grupie badanej, ale nie wykazano powyższych zależności po uwzględnieniu wieku ciężarnej. Obserwowane w grupie otrzymującej mizoprostol niższe wyniki w skali Apgar wymagają dalszych badań.

Artykuł nr 2 opublikowany w „Ginekologii Polskiej"

W artykule drugim analizowano wpływ chorób towarzyszących w trakcie ciąży na preindukcję porodu omawianymi prostaglandynami.

Kobiety, u których zdiagnozowano jakąkolwiek współistniejącą chorobę, miały wyższą masę ciała przy przyjęciu do szpitala – zarówno w grupie dinoprostonu, jak i mizoprostolu – w porównaniu do zdrowych ciężarnych. Ciekawe obserwacje płyną natomiast z porównania liczby przebytych ciąż w grupie kobiet powyżej 35. roku życia, gdzie stwierdzono w obu grupach z chorobami współistniejącymi częściej kobiety w pierwszej ciąży (43,6% vs 28,6% w grupie z dinoprostonem oraz 59,3% vs 35,5% w grupie z mizoprostolem).

Wśród kobiet ze współistniejącą chorobą poród drogą pochwową był obserwowany częściej w grupie dinoprostonu niż mizoprostolu (66,5% vs 52,1%, $p = 0,013$). W konsekwencji cięcia cesarskie obserwowano częściej w grupie mizoprostolu. Co więcej, matki z chorobą po zastosowaniu mizoprostolu – w porównaniu z grupą z dinoprostonem – częściej były kierowane na cięcie cesarskie w trybie nagłym (75% vs 44,1%). Biorąc pod uwagę tylko grupę mizoprostolu, większy odsetek ciężarnych ze współistniejącą chorobą (w porównaniu z kobietami bez choroby) przeszedł cięcie cesarskie (47,9% vs 31,2%; $p = 0,016$), a także więcej z nich przeszło cesarskie cięcie w trybie pilnym (odpowiednio 35,9% vs 20,4%; $p = 0,015$). Szczegółowa analiza, uwzględniająca wiek kobiety z podziałem na poniżej i powyżej 35. roku życia, również wykazała istotnie częściej rozwiązywanie ciąży na drodze cięcia cesarskiego w

podgrupach ze współistniejącą chorobą. Różnic tych nie zaobserwowano w grupie dinoprostonu.

Szczegółowa analiza wskazań do cięcia cesarskiego wykazała, że kobiety ciężarne z chorobą współistniejącą z zastosowanym mizoprostolem częściej prezentowały stan przedrzucawkowy i odklejenie łożyska (zarówno w porównaniu z matkami z chorobą w grupie z dinoprostonem, jak i matkami w grupie z mizoprostolem bez choroby współistniejącej), przy czym najczęstszym wskazaniem był stan zagrożenia płodu (62% – niezależnie od współistnienia choroby). Najczęstsze wskazania w grupie indukowanej dinoprostonem to brak postępu porodu oraz zagrażająca wewnątrzmaciczna zamartwica płodu.

Nie stwierdzono istotnych statystycznie różnic w zakresie powikłań poporodowych w grupie uczestniczek badania, niezależnie od kombinacji prostaglandyn, współistniejącej choroby czy wieku matek, poza częstszą koniecznością nacięcia krocza w grupie z dinoprostonem w porównaniu do grupy z mizoprostolem (40% vs 27%; $p = 0,02$).

Zaobserwowano także, że w grupie z dinoprostonem matki ze współistniejącą chorobą – w porównaniu z matkami bez choroby – wymagały więcej czasu do porodu (tylko droga pochwowa: 39,6 vs 31,3 h; $p = 0,014$ lub jakakolwiek droga: 42,8 vs 35,6 h; $p = 0,023$) oraz do rozpoczęcia porodu (33,5 vs 25,3 h; $p = 0,009$). Po analizie grup z uwzględnieniem wieku matek z podziałem na grupy do i powyżej 35. roku życia nie stwierdzono różnic. Niemniej jednak wykazano, że w grupie kobiet z chorobami towarzyszącymi ciężarne powyżej 35. roku życia w czasie indukcji dinoprostonem charakteryzowały się nieco krótszym, lecz istotnym statystycznie czasem trwania pierwszego okresu porodu (4,4 vs 5,3 h; $p = 0,025$).

Spośród powyższych analizowanych cech żadnych różnic nie zaobserwowano w grupie z mizoprostolem, gdzie średni czas od zastosowania leku do porodu (niezależnie od drogi rozwiązania lub rozwiązane drogami natury) wynosił 12,9 i 12,7 h u kobiet z chorobami towarzyszącymi oraz 14,5 i 15,1 h u ciężarnych bez chorób dodatkowych oraz bez różnic w długości poszczególnych okresów porodu.

Na koniec przeanalizowano wyniki noworodków. W analizie uzyskanych punktacji Apgar jedyną istotną statystycznie różnicę stwierdzono w grupie matek z chorobą, u których zastosowano mizoprostol, ponieważ w tej grupie matki starsze (35+) rodziły dzieci z niższym wynikiem w skali Apgar (9,0 vs 9,7 pkt, $p < 0,001$), a dodatkowo zaobserwowano istotnie wyższy odsetek dzieci z wynikiem Apgar ≤ 6 (7,4% vs 2,2%) i Apgar 7–8 (22,2% vs 3,3%) niż w grupie kobiet poniżej 35. roku życia z chorobami.

W grupie kobiet z dinoprostonem stwierdzono niższą masę urodzeniową dzieci kobiet z chorobą towarzyszącą (3459 g vs 33623 g; p = 0,001) oraz krótszą długość ciała tych noworodków (55,2 vs 56 cm; p = 0,008), bez podobnych obserwacji z podziałem na wiek 35. r.ż. kobiet oraz w grupie indukowanej mizoprostolem. Niemniej jednak, porównując masy urodzeniowe dzieci pomiędzy grupami z dinoprostonem i mizoprostolem, wykazano niższe wartości masy urodzeniowej dzieci w całej grupie z mizoprostolem na poziomie istotności p = 0,011.

Podsumowując, wśród kobiet ze współistniejącą chorobą cięcie cesarskie obserwowano częściej w grupie indukowanej mizoprostolem niż w grupie z dinoprostonem. Natomiast w grupie z dinoprostonem matki ze współistniejącą chorobą – w porównaniu ze zdrowymi kobietami – potrzebowały więcej czasu do rozpoczęcia porodu i do porodu. Nie stwierdzono różnic w powikłaniach poporodowych niezależnie od prostaglandyn, chorób współistniejących czy wieku matek. Noworodki matek w wieku ≥ 35 lat ze współistniejącą chorobą uzyskały niższą średnią punktację w skali Apgar, szczególnie gdy indukowane były mizoprostolem.

Badanie wykazało, że choroby współistniejące wydają się mieć wpływ na ryzyko cięcia cesarskiego w grupie preindukcji mizoprostolem, a także wydłużają czas potrzebny do osiągnięcia aktywnej fazy porodu oraz porodu w grupie dinoprostonu.

Artykuł nr 3 opublikowany w „Ginekologii Polskiej”

Trzeci artykuł dotyczył analizy potencjalnych czynników ryzyka cięcia cesarskiego przy zastosowaniu omawianych prostaglandyn. Porównanie pacjentek podzielonych ze względu na drogę porodu w grupach preindukcji dinoprostonem i mizoprostolem nie wykazało różnic w wieku matki, masie ciała ani BMI przy przyjęciu, obecności niedoczynności tarczycy czy cukrzycy. Statystycznie istotne różnice w grupie z dinoprostonem stwierdzono dla wzrostu matek, ponieważ kobiety wyższe częściej rodziły drogą pochwową (p < 0,01), a z drugiej strony dla nadciśnienia tętniczego, które częściej prowadziło do cięcia cesarskiego w obu grupach (8,3% vs 21,3%; p < 0,001 w grupie z dinoprostonem oraz 9,6% vs 21,2%; p = 0,026 w grupie z mizoprostolem). Nie wykazano różnic w wymiarach miednicy w poszczególnych grupach.

Analiza stanu noworodków wykazuje znaczne różnice w wynikach punktacji w skali Apgar. W obu grupach noworodki urodzone przez cięcie cesarskie otrzymały średnio mniej punktów (p < 0,001), podczas gdy tylko w grupie z mizoprostolem dzieci miały

także niższą masę urodzeniową (3229 g vs 3405 g; p = 0,038) i wiek ciążowy był istotnie statystycznie niższy (38,7 vs 39,3; p = 0,025).

Kolejnym krokiem była analiza możliwych czynników związanych z ryzykiem cięcia cesarskiego we wszystkich trzech grupach (dinoproston, mizoprostol oraz grupa z koniecznością zastosowania obu preparatów) przed indukcją. Pośród ciężarnych z zastosowanym dinoprostonem każdy dodatkowy 1 cm wzrostu powyżej 165 cm oraz każdy dodatkowy 1 cm więcej w wymiarze międzykrętarzowym powyżej 33 cm obniżał ryzyko cięcia cesarskiego (odpowiednio OR 0,93; 95% CI 0,885–0,977; p = 0,004 oraz OR 0,796; 95% CI 0,67–0,94; p = 0,009).

W grupie z mizoprostolem wyższe ryzyko wykazywał wiek kobiety rodzącej powyżej 35 lat (OR 2,51; 95% CI 1,301–4,845; p = 0,006) oraz wiek ciążowy poniżej 38 tygodni (OR 2,024; 95% CI 1,009–4,06; p = 0,047).

Dodatkowo większe ryzyko cięcia cesarskiego wykazało w obu grupach dinoprostonu i mizoprostolu nierództwo kobiety (OR 3,146; 95% CI 1,505–6,573; p = 0,002 i OR 2,492; 95% CI 1,295–4,797; p = 0,006) oraz odpowiednio nadciśnienie tętnicze (OR 2,69; 95% CI 1,233–5,869; p = 0,013 i OR 2,647; 95% CI 1,209–5,794; p = 0,015). Powyższe wyniki zostały potwierdzone w analizie wieloczynnikowej, gdzie wykazano 6,73- i 10,85-krotny wzrost ryzyka cięcia cesarskiego u pierworódek w wieku powyżej 35 lat – odpowiednio zarówno w grupie dinoprostonu, jak i mizoprostolu.

W badaniu wykazano brak wpływu na ryzyko cięcia cesarskiego innych analizowanych parametrów, takich jak: masa ciała matki, BMI, pomiary obwodu brzucha i miednicy (poza wymiarem międzykrętarzowym), historia poronień, szacowana masa płodu, cukrzyca, niedoczynność tarczycy, stan kolonizacji *Streptococcus agalactiae*.

Wnioski

Wniosek główny:

Niniejsza praca doktorska, porównująca dwie prostaglandyny zastosowane do farmakologicznej preindukcji porodu – dinoproston i mizoprostol, po uwzględnieniu skuteczności, ale przede wszystkim bezpieczeństwa obu preparatów, wskazuje większą korzyść stosowania dinoprostonu w grupie kobiet w zaawansowanym wieku definiowanym powyżej 35. roku życia.

Wnioski szczegółowe:

1) zastosowanie mizoprostolu ponad dwukrotnie zwiększa szansę oraz skraca czas do rozpoczęcia porodu oraz przeprowadzenia porodu niezależnie od sposobu rozwiązania – drogami natury lub cięciem cesarskim niezależnie od wieku ciężarnej, liczby przebytych porodów czy stanu szyjki macicy,

2) w grupie kobiet po 35. roku życia nie wykazano różnic w czasie niezbędnym do rozpoczęcia akcji porodowej czy samego porodu niezależnie od sposobu rozwiązania, porównując obie prostaglandyny,

3) choroby współistniejące wydają się zwiększać ryzyko cięcia cesarskiego w indukowanej mizoprostolem grupie kobiet po 35. roku życia,

4) choroby współistniejące wydają się wydłużać czas potrzebny do wywołania akcji porodowej oraz do porodu niezależnie od rodzaju drogi rozwiązania w grupie indukowanej dinoprostonem,

5) indukcja mizoprostolem w grupie kobiet z chorobami towarzyszącymi skutkowała niższą punktacją w skali Apgar u noworodków kobiet powyżej 35. roku życia,

6) w grupie indukowanej mizoprostolem wiek kobiety powyżej 35. roku życia oraz wiek ciążowy poniżej 38. tygodnia ciąży stanowią czynniki ryzyka cięcia cesarskiego,

7) nierództwo i nadciśnienie tętnicze są czynnikami ryzyka konieczności rozwiązania ciąży cięciem cesarskim niezależnie od metody preindukcji mizoprostolem czy dinoprostonem.

Streszczenie pracy w języku angielskim

Introduction

The most important goal of labor induction is to improve the perinatal outcomes for both the newborn and the mother. Successful induction of labor is considered when vaginal delivery is completed within 24 hours without maternal complications and a neonate with a high (≥8 points) Apgar score. Finding a safe, fast and effective method of labor induction is a key part of the growing demand for active prenatal care, as nearly 40% of pregnant women may have the need of induction of labor[1]. The decision on the right moment to finish the pregnancy, which would be the best for both the baby and the mother, has always been, and still is, a matter of debate[2].

In the era of postponing pregnancy and giving birth to a child at an advanced age, which has both social and economic conditions, various aspects of such decisions has to be taken into account. Young women are usually healthy, but older pregnant women, especially those over 40, are at increased risk of comorbidities such as high blood pressure, diabetes and obesity[3].

Pre-induction and induction of labor – indications and contraindications

The indications and contraindications for the induction of labor procedure are generally accepted in medical world, and a group of factors influencing its effectiveness has already been estimated. Maternal indications include: pregnancy-induced hypertension, pre-eclampsia, chronic hypertension, diabetes mellitus, chronic diseases of a pregnant woman resistant to treatment, serological conflict and fetal indications: intrauterine infection, fetal hypotrophy, abnormal test results that may suggest impaired fetal hypoxia (e.g. abnormal CTG, borderline values of Doppler flow in the fetal vessels), premature rupture of the membranes, fetal malformations, history of intrauterine death of the term fetus. The age of the pregnant woman over 40 years old has also become a new indication between 39 and 40 weeks of pregnancy[4].

Both the Polish and the Canadian Society of Gynecologists and Obstetricians, among the clinical situations that preclude the safe natural birth and at the same time are the contraindications to induction of labor, mention: placenta or vasa previa, abnormal position of the fetus (transverse or pelvic), active genital infection with herpes simplex virus, abnormal measurements of the patient's pelvis, invasive cervical cancer, as well

as the medical history data, like: previous classical cesarean section or inverted T-incision of the uterus, myomectomy and rupture of the uterus[4,5].

Pre-induction and induction of labor – methods

According to the commonly accepted definition, induction of labor is a series of activities aimed at initiating contractile activity of the uterine muscle in a pregnant woman before its initial onset and, as a result, giving natural birth to a child[6].

In the most cases, the decision to induce labor is, however, associated with the immaturity of the cervix to delivery and it becomes necessary to pre-induce labor first. Labor pre-induction is a series of activities aimed at accelerating the maturation of the cervix, which means its shortening, opening and changing the consistency. Modern medicine has developed only a few tools able to influence the condition of the cervix, which can be briefly divided into mechanical and pharmacological methods. Among the mechanical methods, the most commonly used is the Foley catheter, which is inserted aseptically through the cervical canal above its internal end and filled with physiological saline solution. This method involves mechanically irritating the inner end of the cervix, stretching the lower uterus and stimulating the secretion of endogenous prostaglandins that physiologically maturate the cervix. It can be used for women after cesarean section.

Pharmacological methods include prostaglandins E1 and E2, and much less frequently used: mifepristone, glycocorticosteroids, estrogens, hyaluronidase, relaxin, nitric oxide donors. Prostaglandin E2 – dinoprostone has recently become the only substance used for pharmacological pre-induction in Poland. It is a natural factor produced by the temporal and amniotic membrane, it causes the relaxation of the collagen fibers of the cervix and causes contraction of the uterine muscle itself[7]. Misoprosol is a synthetic analogue of prostaglandin E1 and shows the cervical activity and induction of labor property. Vaginal PGE1 has been shown to be a more effective method of vaginal delivery within 24 hours compared to placebo, but it increases the risk of uterine hyperstimulation without abnormal fetal heart rhythm[8]. In Poland, this medicament was registered for the pre-induction of live labor for several years, so there are very few studies focused on it, especially in the group of patients over 35 years of age.

The intravenously administrated oxytocin is currently the most frequently used method in inducing the delivery of a fetus. Administration of oxytocin should be precise,

preferably with the usage of an infusion pump, and the continuous monitoring of the fetus during the infusion is recommended. In pregnant women after cesarean section, after analyzing the obstetric situation, it is possible to (cautiously) use oxytocin stimulation of labor[9].

The choice of the method, in accordance with the recommendations of the Polish Society of Gynecologists and Obstetricians, is based mainly on the assessment of the obstetric condition of each patient, the preferences of the deciding physician and, most often, the availability of a given procedure in a hospital. In current practice, no method of accelerating cervical maturation appears to be superior to others given their overall efficacy and safety, indicating that the ideal method of pre-induction of labor is still to be found and the question of which method to choose to reduce the risk of cesarean section and to improve the perinatal outcome is still open.

Pre-induction and induction of labor – factors influencing the effectiveness of the procedure

Induction of labor as a medical procedure may involve several complications, of which the pregnant woman should be always forewarned; informed written consent of the patient for the procedure should also be obtained. Failure of induction should be considered as the lack of effectiveness, requiring a temporary postponement and re-conduct of the procedure, or the need to end pregnancy by caesarean section, especially urgent one – in the event of a life-threatening condition of the fetus or the patient. Such a situation may occur, inter alia, by the appearance of uterine hyperstimulation with or without fetal heart rhythm disturbances, umbilical cord prolapse, uterine rupture, inflammation of the membranes, exhaustion of the patient's strength[5,10].

It is extremely important to know the factors which determine the success of the procedure, and even more importantly to identify the risk factors of failure of the induction of labor. Undoubtedly, the most important thing is the condition of the cervix and its maturity. Other proposed factors adversely affecting the course of induction of labor and leading to cesarean section, include: body mass index BMI > 40 kg/m^2, estimated fetal weight over 4000 g or gestational diabetes[11].

Other studies indicate factors influencing the course of labor like: the woman's age, the number of deliveries or the use of epidural anesthesia, and the type of labor induction method[12]. The list is certainly much longer, so the research is still being carried out to

establish them, and most importantly, to isolate the modifiable factors, which can then be treated preventively.

Work summary

Introduction

The age of the woman giving birth has recently become a new indication for induction of labor, due to the increasing number of maternal and fetal complications, including the intrauterine foetal death, of which the risk increases with the age of the pregnant woman and the duration of pregnancy[13-16]. The reasons for the observed dependencies are still unknown. Some researchers believe that in the group of 40-year-old women, the 39th week of pregnancy can be considered as a biologically mature pregnancy and labor induction should be considered in order to end the pregnancy[17]. Developing the safest and most beneficial method of labor induction in patients of advanced age defined as 35 years of age and more is an extremely important and still open task. Too little research has been done on induction of labor in this age group of patients, which is associated with many unknowns regarding both the choice of the best procedure and the timing of its implementation.

Objectives

The goal of the presented dissertation is determining whether one of the two prostaglandins, dinoprostone or misoprostol, outweighs the other in terms of efficacy and safety, used as a method of induction of labor in women of advanced age defined as 35 years of age and older.

Detailed objectives:

- evaluation of the effects and comparison of two methods of pharmacological pre-induction of labor (dinoprostone and misoprostol) and development of the optimal method of combining these methods,

- assessment of whether the presence of the disease during pregnancy affects the efficacy and safety of pre-induction with dinoprostone or misoprostol,
- determination of risk factors for caesarean section using the above-mentioned prostaglandins.

Efficacy was measured as a time from the initiation of treatment to the onset of labor and delivery, while safety was measured by the frequency of emergency cesarean sections, the presence of complications in delivery, and a few health indicators in newborns.

Material

The study included 560 pregnant women hospitalized at the Department of Obstetrics and Perinatology of the University Hospital in Krakow from January 2015 to April 2019. All articles are based on a retrospective cohort analysis based on the hospital's archival medical documentation.

The main criteria for the inclusion of patients were: single pregnancy, longitudinal presentation of the fetus, medical indication for labor induction. Other inclusion criteria were a Bishop score of ≤ 4 and no active labor prior to dosing.

The exclusion criteria included the following: patients with an estimated fetal weight above 4500 g, placenta previa, vasculature anterior, any other known contraindications to vaginal delivery, or any contraindications to the use of prostaglandins such as previous uterine surgery or caesarean section.

The following data were assessed: mother's age, body weight at admission with height and Body Mass Index (BMI), number of pregnancies, history of births, miscarriage history, gestational age and estimated fetal weight according to the ultrasound measurement, method of delivery, indications for caesarean section, the need for curettage of the uterine cavity after vaginal delivery, perineal incision, perineal rupture, anemia requiring blood transfusion, appearance of uterine hyperstimulation, presence or absence of Streptococcus agalactiae in the vagina and / or anus, pelvic dimensions and abdominal circumference of pregnant women. In addition, the baby's gender and newborn scores were recorded, including Apgar score, birth weight, and birth length.

The most frequently reported comorbidities in pregnant women were: diabetes mellitus, hypertensive diseases, intrahepatic cholestasis in pregnancy, asthma, thrombocytopenia and hypothyroidism.

Methods

Labor pre-induction was carried out with the use of a 0.5 mg dinoprostone gel (Prepidil, Pfizer Polska Sp. z o.o.) or a vaginal insert with misoprostol at a dose of 0.2 mg (Misodel, Ferring Pharmaceuticals Poland Sp. z o.o.). The allocation of the patient to the medicament depended on the preferences of the doctor qualifying for the procedure or the availability of the drug at a given moment in the Department, without the possibility of retrospectively establishing the specific selection criteria.

The following were analyzed: the indications for induction of labor, time from drug administration to vaginal delivery or time to any delivery (vaginal or caesarean) and time to delivery, the maternal complications: perineal incision, perineal rupture, detachment or retention of placenta, and anemia requiring blood transfusion and neonatal – Apgar score.

In article 1, all patients with concomitant diseases were excluded from the study, thus the groups obtained were pregnant with a physiological course of pregnancy, where gestational age was the most often indication for labor induction. In the group of 240 patients obtained in this way, 93 pregnant women received misoprostol and 147 dinoprostone, while in the latter subgroup of 39 women received additional misoprostol due to the lack of response to dinoprostone.

In article no. 2 from the entire group of 560 pregnant women, a group of 320 women with at least one diagnosed disease was selected for a detailed analysis, of which 117 received misoprostol and 203 dinoprostone. In both groups, there were 57 and 87 women with hypothyroidism, 27 and 28 with hypertension, 23 and 65 with diabetes, respectively, and 3 and 15 women with both diabetes and hypertension, and 7 and 8 women with other diseases, respectively. Among pregnant women without additional diseases, 93 received misoprostol and 147 dinoprostone. In the dinoprostone group, 100 women were identified, who additionally received misoprostol as a second drug. In each group, women over and under 35 were also distinguished.

In article no. 3, the entire research group of 560 pregnant women was qualified for the study. All patients were divided according to the pre-induction method, obtaining a group that received dinoprostone (group D; 250 people) or misoprostol (group M; 210 people) and a third group of pregnant women, which required the introduction of a

second prostaglandin, first dinoprostone, and then misoprostol (group D + M; 100 people) to achieve the desired effect.

Oxytocin infusion was used to enhance uterine contractions. Fetal heart rate was monitored with cardiotocographic records.

Statistical analysis

The statistical analysis was carried out in accordance with the applicable requirements for scientific research in medicine. In the part presenting the characteristics of the women covered by the study, depending on the nature of the presented features (variables), the descriptive characteristics are presented by giving percentages (for categorized features) and means with standard deviation and medians with interquartile range (for continuous variables). To determine the statistical significance of differences between the groups, the following tests were used: chi-square or if the assumptions were not met, the Fisher's exact test – for categorized variables. In the case of continuous variables, in the first steps, compliance with the normal distribution was verified using the Shapiro-Wilk test, and then, depending on whether the compliance requirement was met or not, the appropriate Student's or U-Mann-Whitney tests.

For the purposes of article 1, an Intent to Treat (ITT) analytic strategy was used to determine the difference in efficacy between dinoprostone and misoprostol in view of the prospective nature of the follow-up. The main conclusions were based on the Cox proportional regression model results. The use of this model allowed to determine the differences between the studied drugs in the effective delivery of labor over time, while eliminating potential confounding variables such as obstetric history, maternal age, the degree of cervical maturity at the time of drug administration or the use of oxytocin. The obtained risk hazard score (HR) determines how much the use of misoprostol increases the chance of successful delivery over time. In addition, this article uses an analysis of variance (ANOVA) model with interaction term to answer the question whether the differences observed between different drugs in the duration of induction of labor depend on the age of the pregnant woman.

In article 2, as in article 1, the analysis was carried out in groups according to the ITT strategy. The analysis techniques described above were used to assess the presence of differences in the duration of labor induction and in the occurrence of defined endpoints depending on the treatment applied or depending on the presence of comorbidities in

pregnant women. Additionally, in order to answer the question whether the observed differences between pregnant women without comorbidities compared to pregnant women with comorbidities are different in mothers younger than 35 than in mothers aged 35 and over, the Cochran-Mantel-Haenszel statistic was used.

In article 3, taking into account that its aim was to determine the risk factors for caesarean section depending on the pre-induction method used, the analysis was carried out in the scheme of a nested prospective case-control study in which pregnant women who gave birth by caesarean section were compared with pregnant women giving birth to natural forces. A logistic regression model was used to identify risk factors. This model allowed for the determination of independent risk factors (after elimination of significant confounding variables), showing how much the risk of cesarean section is increased (or decreased) in the presence of a specific feature in the mother when dinoprostone, misoprostol or both of these drugs were used.

Summary of the results

Article 1 published in "Ginekologia Polska"

The first article focuses on assessing the effectiveness in inducing labor after the use of dinoprostone and misoprostol for labor pre-induction. In the study, intervention with misoprostol resulted in vaginal delivery in 68.8% of cases, compared with 76.9% in the dinoprostone group ($p = 0.207$). It was shown that the use of misoprostol significantly shortened both the time to start (9.9 vs 25.3 hours, $p < 0.001$) and to the end of labor compared to the used dinoprostone gel (regardless of the final method of delivery – vaginal delivery or caesarean section: 14.5 vs 35.6 hours, $p < 0.001$ and only by natural route: 15.1 vs 31.1; $p < 0.001$). In addition, the Cox regression model showed that misoprostol more than twice has risen the chance of starting labor and childbirth compared to dinoprostone, also after taking into account the variables potentially influencing the outcome, such as the woman's age, number of pregnancies, cervical condition and the use of oxytocin. Significantly more pregnant women required an additional supply of oxytocin to enhance labor in the group treated with dinoporostone (37.4%) compared to the group with misoprostol (8.6%; $p < 0.001$).

Interestingly, a detailed analysis of the women according to the age did not repeat the results obtained for the entire group. The study did not show that the age of a pregnant woman affects the effectiveness of prostaglandins used, or at the beginning of labor, to the birth of a newborn or the duration of the second stage of labor.

Potential adverse effects, both for the mother and the fetus, have been studied in detail. The frequency of the caesarean sections, indications for the procedure, and maternal complications did not differ significantly between the study groups. Only in the misoprostol-induced group, a higher frequency of fetal heart rhythm disturbances requiring urgent caesarean section was found, although not statistically significant. In the analysis of neonatal data in the misoprostol group, worse Apgar scores (9.4 vs 9.8; $p = 0.41$), lower birth weights (3385 g vs 3623 g; $p < 0.001$) and neonatal length (54.9 cm vs 56 cm) were observed. ; $p = 0.008$), which may be partly due to the statistically lower gestational age of patients (39.7 vs 40.6; $p < 0.001$) in this group compared to the dinoprostone group.

In the study, the analysis of the factors that could potentially influence the effect of each intervention showed no differences between the groups in terms of maternal age, number of births, prior natural delivery, miscarriage history, patient BMI, pre-drug Bishop score, or estimated fetal weight.

The study showed that the use of a vaginal insert with misoprostol compared to dinoprostone gel seems to increase the chance of childbirth and shorten the time to the onset of the first stage of labor and duration of labor in the entire study group, with no influence of mothers' age. The lower Apgar scores in the misoprostol group require further studies.

Article 2 published in "Ginekologia Polska"

The second article analyzes the influence of comorbidities during pregnancy on the pre-induction of labor with the described prostaglandins.

Women diagnosed with any comorbid disease had higher body weights on admission to the hospital in both the dinoprostone and misoprostol groups compared to healthy pregnant women. Interesting observations are drawn from the comparison of the number of pregnancies in the group of women over 35 years of age. In both groups with comorbidities these women were found more often in their first pregnancy (43.6% vs 28.6% in the group with dinoprostone and 59.3% vs 35.5% in the misoprostol group).

Among women with coexisting disease, vaginal delivery was observed more often in the dinoprostone group than in the misoprostol group (66.5% vs 52.1%, p = 0.013). As a consequence, cesarean sections were seen more frequently in the misoprostol group. Moreover, mothers with the disease after using misoprostol compared to the group with dinoprostone were more often referred to emergency caesarean section (75% vs 44.1%). Considering only the misoprostol group, a greater proportion of pregnant women with coexisting disease (compared to women without the disease) underwent caesarean section (47.9% vs 31.2%; p = 0.016), and more of them underwent urgent caesarean section (35.9% vs 20.4%, respectively; p = 0.015). These differences were not observed in the dinoprostone group. A detailed analysis of indications for caesarean section showed that pregnant women with a disease coexisting with misoprostol more often presented with pre-eclampsia and placental detachment (both compared to mothers with the disease in the group with dinoprostone and mothers in the group with misoprostol without comorbid disease), with the most common indication was fetal distress (62% – regardless of the coexistence of the disease). In the dinoprostone induced group, the most frequent indications were the lack of progress in labor and the risk for the fetus.

There were no statistically significant differences in postpartum complications in the group of study participants, regardless of the combination of prostaglandins, comorbid disease or maternal age, except for more frequent incision of the perineum in the dinoprostone group compared to the misoprostol group (40% vs 27%; p = 0, 02).

It was also observed that in the group with dinoprostone, mothers with coexisting disease compared to mothers without disease required longer time to delivery (vaginal only: 39.6 vs 31.3 hours; p = 0.014 or any route: 42.8 vs 35.6 hours; p = 0.023) and time to the onset of labor (33.5 vs 25.3; p = 0.009). After analyzing the age of the mothers, no differences were found. The above differences were also not observed in the group with misoprostol, where the mean time from drug application to delivery (regardless of the route of delivery or delivered naturally) was 12.9 and 12.7 hours in women with comorbidities and 14.5 and 15.1 hours in pregnant women without additional diseases.

Finally, the results of the newborns were analyzed. In the analysis of the Apgar score, the only statistically significant difference was found in the group of mothers with the disease treated with misoprostol, because in this group older mothers (35+) gave birth to children with a lower Apgar score (9.0 vs 9.7 points, $p < 0.001$) and additionally, a significantly higher percentage of children with Apgar ≤ 6 (7.4% vs 2.2%) and Apgar

7–8 (22.2% vs 3.3%) scores were observed in that group than in the group of women under 35 with diseases.

In conclusion, in women with coexisting disease, caesarean section was observed more often in the misoprostol-induced group than in the dinoprostone group. On the other hand, in the group with dinoprostone, mothers with comorbid disease, compared to healthy women, needed more time to give birth and to start labor. There were no differences in postpartum complications regardless of prostaglandins, comorbidities or maternal age. Newborns of mothers ≥ 35 years of age with coexisting disease had lower mean Apgar scores.

Our study showed that comorbidities appear to affect the risk of caesarean section in the Misoprostol pre-induction group, and also increase the time needed to achieve active labor and delivery in the Dinoprostone group.

Article 3 published in "Ginekologia Polska"

The third article analyzed potential risk factors for caesarean section with the use of two prostaglandins. Comparison of patients divided according to the route of delivery in the pre-induction groups with dinoprostone and misoprostol showed no differences in maternal age, body weight or BMI at admission, the presence of hypothyroidism or diabetes. Statistically significant differences in the group with dinoprostone were found for maternal height, as taller women more often gave birth vaginally ($p < 0.01$) and, on the other hand, hypertension, which more often led to caesarean section in both groups (8.3% vs 21, 3% $p < 0.001$ in the dinoprostone group and 9.6% vs 21.2%; $p = 0.026$ in the misoprostol group). There were no differences in pelvic dimensions between groups. The analysis of the condition of the newborns shows significant differences in the Apgar scores. In both groups, newborns delivered by cesarean section received on average fewer points ($p < 0.001$), while only in the misoprostol group the children also had lower birth weight (3229 g vs 3405 g; $p = 0.038$) and the gestational age was statistically significantly lower (38.7 vs 39.3; $p = 0.025$).

The next step was to analyze the possible factors associated with the risk of cesarean section in all three groups (dinoprostone, misoprostol and the group requiring both medicaments) before induction. Among pregnant women with the use of dinoprostone, each additional 1 cm of height above 165 cm and each additional 1 cm more in the interclavicular dimension above 33 cm reduced the risk of cesarean section (OR 0.93;

95% CI 0.885-0.977; p = 0.004 and OR 0.796; 95% CI 0.67-0.94; p = 0.009, respectively).

In the group with misoprostol, the higher risk was shown by the age of the woman giving birth over 35 years (OR 2.51; 95% CI 1.301-4.845; p = 0.006) and the gestational age below 38 weeks (OR 2.024; 95% CI 1.009-4.06; p = 0.047).

In addition, a higher risk of cesarean section was shown in both the dinoprostone and misoprostol groups of nullipara women (OR 3.146; 95% CI 1.505-6.573; p = 0.002 and OR 2.492; 95% CI 1.295-4.797; p = 0.006) and hypertension (OR 2.69; 95% CI 1.233-5.869; p = 0.013 and OR 2.647, 95% CI 1.209-5.794; p = 0.015) respectively. The above results were confirmed in a multivariate analysis, which showed a 6.73 and 10.85-fold increase in the risk of cesarean section in primiparous women over 35 years of age, in the dinoprostone and misoprostol groups, respectively.

Our study showed no effect on the risk of cesarean section of other analyzed parameters, such as: maternal weight, BMI, measurements of the abdominal and pelvic circumference (except the intertrochanteric dimension), miscarriage history, estimated fetal weight, diabetes, hypothyroidism, colonization status of Streptococcus agalactiae.

Conclusions

Main conclusion:

After taking into account the efficacy and safety of two prostaglandins used for pharmacological pre-induction of labor - dinoprostone and misoprostol, the research shows a greater benefit of using dinoprostone in the group of women at an advanced age defined above 35 years of age.

Detailed conclusions:

1) the use of misoprostol rises more than twice not only the chance but also shortens the time to start labor and delivery itself, regardless of the method of delivery - via vaginal delivery or cesarean section, regardless of the pregnant age, number of deliveries or the condition of the cervix,

2) in the group of women over 35, there were no differences in the time necessary to start labor or the delivery itself, regardless of the method of delivery, comparing both prostaglandins,

3) comorbidities seem to increase the risk of caesarean section in misoprostol-induced women over 35 years old,

4) comorbidities seem to lengthen the time needed to induce labor and delivery, regardless of the type of delivery route in the dinoprostone-induced group,

5) induction with misoprostol in the group of women with comorbidities resulted in lower Apgar scores in newborns of women over 35 years old,

6) in the misoprostol-induced group, the age of the woman over 35 and the gestational age below 38 weeks of pregnancy are risk factors for cesarean section,

7) nulliparity and arterial hypertension are the risk factors for the need to end the pregnancy by cesarean section, regardless the method of pre-induction with misoprostol or dinoprostone.

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Comparison of Misoprostol versus Dinoprostone for delivery induction among pregnant women without concomitant disease

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ABSTRACT

Objectives: Induction of labour is a part of an active prenatal care nowadays and the ideal method of that procedure still remains to be identified. The purpose of this study was to evaluate effectiveness of misoprostol vaginal insert as compared to dinoprostone gel for delivery induction in pregnant women without any comorbidities.

Material and methods: It was a retrospective cohort study of 240 pregnant women. The primary study outcome was successful delivery. Other analysed parameters included time to delivery of a baby, time to the beginning of the first stage of labour, time to vaginal delivery, and duration of all delivery stages. We compared both methods regarding maternal complications during and after delivery. We also reviewed neonatal outcomes such as birth weight, birth length and 1-minute Apgar scores.

Results: The patients' basic characteristics were similar regarding their age, gravidity, parity, height, weight and Bishop score. Time to any delivery and to the onset of a labour in the misoprostol group versus in the dinoprostone group was 14.5 vs 35.6 h ($p < 0.001$) and 9.9 h vs 25.3 h ($p < 0.001$) respectively. The chance of the beginning of labour and the baby's delivery over time has been observed to be approximately two times higher for misoprostol as compared to dinoprostone.

Conclusions: Our study showed that using misoprostol vaginal insert in comparison to dinoprostone seems to shorten the time to beginning of the first stage of labour as well as the time to the delivery itself. Some lower Apgar scores observed in the misoprostol group requires further investigation.

Key words: misoprostol; dinoprostone; induction of labor

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INTRODUCTION

Finding a safe, quick and effective method of labour induction is a crucial part of a growing need for active prenatal care. Decision on the right moment to complete a pregnancy that would be the best for both the baby and the mother has been always a debatable issue. Modern medicine has developed only a few tools to manage an unfavourable cervix which may be shortly divided into mechanical and pharmacological methods of preinduction. In the final step, induction of delivery involves oxytocin administration which strengthens the uterine contractions leading to childbirth. In current practice, no cervical ripening method appears superior to the others considering their overall effectiveness and safety outcomes [1], which indicates that the ideal method of labour preinduction remains to be identified. Prostaglandins are commonly used in obstetrics nowadays. Dinoprostone is a natural E2 prostaglandin produced by decidua and amnion, it causes relaxation of cervical collagen and develops uterine fibres contractions [2]. Misoprostol is a synthetic analogue of E1 prostaglandin and, although it was originally registered as a drug in the prevention and treatment of stomach ulcer disease [3], nowadays it is widely used in obstetrics also in preinduction of labour [4].

Objectives

The purpose of this study was to evaluate effectiveness and safety of misoprostol vaginal insert at a dose of 0.2 mg (Misodel, Ferring Pharmaceuticals Poland sp. z o.o) as compared to dinoprostone gel at a dose of 0.5 mg (Prepidil, Pfizer Polska Sp. z o.o.), administered in daily clinical practice for delivery induction in pregnant women without any comor-

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bidities. Additionally, we evaluated whether mothers' age affected clinical outcomes.

MATERIAL AND METHODS

It was a retrospective cohort study that included pregnant women requiring labour induction for either medical or obstetric indications, hospitalized at the Obstetric and Perinatology Department at the University Hospital in Cracow between January 2015 and April 2019.

Inclusion criteria were (1) singleton gestation, (2) cephalic foetus presentation, (3) full-term pregnancy, (4) Bishop's score ≤ 4, (5) reactive foetal heart rate (FHR) pattern, and (6) lack of spontaneous uterine contractions before administration of the drug.

Patients were excluded for the following reasons: (1) malpresentation, (3) estimated foetal weight > 4500 g (4) placenta previa or unexplained vaginal bleeding, (5) vasa previa, (6) other known contraindications to vaginal delivery, (7) any contraindication to receiving prostaglandins, (8) previous caesarean delivery or uterine surgery, (9) preterm delivery. Other exclusion criteria included maternal comorbidities such as: hypertension, diabetes mellitus, intrahepatic cholestasis of pregnancy, asthma, and thrombocytopenia.

The primary study outcome was successful vaginal delivery. Other analysed parameters included time from drug administration to vaginal delivery, to any (vaginal or by Caesarean section) delivery, and time to the onset of labour defined as regular uterine contradictions at least every ten minutes with evidence of change in cervical dilatation or cervical effacement, and duration of all delivery stages. We also reviewed neonatal outcomes such as birth weight, birth length and 1-minute Apgar score. Finally, we analysed potential delivery complications like a necessity of emergency Caesarean section, placenta abruption, placenta arrest and a necessity of uterine curettage after vaginal birth, as well as episiotomy and anaemia requiring blood transfusion.

Statistical analysis

The study group consisted of women who received misoprostol, dinoprostone, and both (after dinoprostone was ineffective the misoprostol was used in some women). Thus, there were three groups of mothers. The first part of the analysis, which is intended to compare successful labour inductions after the implementation of one drug only, presents differences between 'misoprostol only' and 'dinoproston only' groups. In order to compare basic characteristics of the study groups for interval scale variables [age, time, weight, body mass index (BMI)], first normal distribution in groups was assessed by Shapiro-Wilk test, and then for normally distributed variables the t-test for equal or unequal variances, and for skewed variables the U-Mann-Whitney test were used to assess significance. Chi-squared Person's test was used for nominal or ordinal scale variables provided that the expected value of at least five was observed in each cell, otherwise the exact Fisher's test was performed. As a next step, to reveal whether there is a difference in the effectiveness between implemented drugs an intention to treat (ITT) approach was implemented — meaning mothers started with misoprostol were considered as the first group, and mothers started with dinoproston as the second group irrespective of whether the mother was given later the other drug for induction purposes or not. The proportional Cox regression model was performed to assess the strength of difference between misoprostol and dinoprostone in the effectiveness of delivery upon time. The calculated hazard ratio shows how many times the delivery is more or less likely in a specified amount of time. Models were created as both unadjusted and adjusted for the clinically important covariates. In addition, it was tested a possible impact of woman's age on the efficacy of the treatment. For that purpose, firstly, a linear regression of the mother's age on the time between drug implementation and the beginning of labour or the delivery of a baby, and additionally the second stage of labour, with the treatment type covariate were performed. Secondly, to check whether the difference between misoprostol and dinoprostone depended on mother's age (the test for a modification effect of the mother's age < 35, and 35+) the interaction terms between categorised mother's age and a group type variable in the ANOVA models were used. All the analyses were done using the IBM SPSS Statistics version 25. Pairwise procedure was used for missing data. Results (differences) were considered statistically significant if the p-value was less than 0.05.

RESULTS

There were 560 pregnant women identified in medical records as admitted to the Obstetric and Perinatology Department at the University Hospital in Cracow, Poland for induction of delivery in the period from January 2015 till April 2019. Out of 560, 320 were excluded due to the presence of any of the co-morbidity mentioned under the exclusion criteria. In the remaining 240 women there were 93 women who received misoprostol and 147 who were given dinoprostone. In the last-mentioned group, however, there were 39 (26.5%) which were observed as not-reacting to the drug, and they received after some time misoprostol additionally. Thus "one drug successful labour induction" groups included 201 pregnant women, out of whom 93 (46.3%) were treated with misoprostol and 108 (53.7%) were given dinoprostone.

The basic characteristics of mothers were similar across study groups regarding their age, gravidity, parity, weight, and BMI at admission. There were no statistically significant differences in pre-ripening cervical characteristics either, or the initial Bishop score in all patients was ≤ 4 (Tab. 1). Consid-

Table 1. Clinical characteristics of the study groups (across "after one drug successful delivery" groups)

	Misoprostol [n = 93]	Dinoprostone [n = 108]	Significance
Maternal age [years] Mean, (SD) Median (Q1–Q3)	 31.1 (4.4)* 31.0 (28.5–34.0)	 30.6 (4.9) 30.0 (28.0–34.0)	$p^{MW} = 0.293$
Weight at admission [kg] Mean, (SD) Median (Q1–Q3)	[n = 47]* 76.8 (10.9) 75.0 (69.0–83.0)	[n = 63] 78.8 (13.1) 77.0 (70.0–86.0)	$p^{MW} = 0.385$
Height [cm] Mean, (SD) Median (Q1–Q3)	[n = 84] 165.7 (5.7) 166.5 (162.0–170.0)	[n = 97] 167.3 (5.9) 168.0 (164.0–171.0)	$p^{t-e} = 0.054$
Body mass index at admission [kg/m^2] Mean, (SD) Median (Q1–Q3)	[n = 46] 28.5 (3.7)* 27.4 (25.9–30.4)	[n = 63] 27.9 (4.3) 27.1 (24.8–30.1)	$p^{MW} = 0.406$
Number of pregnancies [n, (%)]			df = 2 $p^{chi2} = 0.713$
1	52 (55.9%)	66 (61.1%)	
2	20 (21.5%)	22 (20.4%)	
≥ 3	21 (22.6%)	20 (18.5%)	
Parity history (current delivery included) [n (%)]			df = 2 $p^{chi2} = 0.854$
1	64 (68.8%)	77 (71.3%)	
2	18 (19.4%)	21 (19.4%)	
3	11 (11.8%)	10 (9.3%)	
Nulliparous [n, (%)]	62 (66.7%)	76 (70.4%)	df = 1 $p^{chi2} = 0.648$
Miscarriage history [n, (%)]			df = 1 $p^{chi2} = 0.305$
No	70 (75.3%)	88 (81.5%)	
Yes	23 (24.7%)	20 (18.5%)	
Pre–ripening cervical characteristics [n (%)]			
Dilatation ≤ 1 cm	86 (92.5%)	99 (91.7%)	df = 1 $p^{chi2} = 0.999$
Effacement ≤ 50%	85 (91.4%)	101 (93.5%)	df = 1 $p^{chi2} = 0.600$
Gestational age [weeks]# Mean, (SD) Median (Q1–Q3)	 39.7 (1.8)* 40.6 (38.9–40.9)	 40.6 (0.7)* 40.9 (40.5–41.0)	$p^{MW} < 0.001$
Estimated birth weight [g] Mean, (SD) Median (Q1–Q3)	[n = 54] 3325 (552)* 3450 (3000-3748)	[n = 37] 3588 (413) 3682 (3233-3883)	$p^{MW} = 0.027$

*p < 0.05 by the Shapiro-Wilk test for normal distribution; #at a time of administration of the first dose of the drug; MW — the U-Mann-Whitney test; t-e — the Student's t-test for equal variances; chi2 — the chi-squared test, df — degrees of freedom; F — the exact Fisher's test

ering gestational age, it was slightly lower in the misoprostol group as compared to dinoprostone group (medians: 40.6 vs 40.9 weeks respectively, p < 0.001), additionally, estimated birth weight was also lower in the misoprostol group (medians: 3450 vs 3682 g, respectively, p = 0.027). The indications for labour induction did not differ significantly between the two groups, although Rh incompatibility was observed slightly more frequently in the dinoprostone group (4.1% vs 1.1%) and foetal indications (including foetal growth restriction) were noticed more frequently in the misoprostol group (16.1% vs 8.2%). Most inductions were initiated due to prolonged pregnancy exceeding the term date. There was no operative vaginal delivery.

The proportion of mothers who underwent vaginal delivery was comparable between the groups, as it was 68.8% in the misoprostol and 76.9% in the dinoprostone group (p = 0.207). There were also no differences between the rate of Caesarean section or indications for such delivery between the two groups. The most often causes of Caesarean section were foetal distress seen in cardiotocography

Table 2. Mode of delivery and indications for caesarean section across "after one drug successful delivery" groups

	Misoprostol [n = 93]	Dinoprostone [n = 108]	Significance
Cesarean section	29 (31.2%)	25 (23.1%)	df = 1 $p^{chi2} = 0.207$
Emergency Caesarean delivery out of total deliveries	19 (20.4%)	10 (9.3%)	df = 1 $p^{chi2} = 0.028$
Emergency Caesarean delivery out of total Caesarean sections	[n = 29] 19 [65.5%]	[n = 25] 10 [40.0%]	df = 1 $p^{chi2} = 0.100$
Vaginal delivery	64 (68.8%)	83 (76.9%)	df = 1 $p^{chi2} = 0.207$
Indications for Caesarean section	[n = 29]	[n = 25]	$p^{F} = 0.207$
Foetal distress	18 (62.1%)	10 (40.0%)	
Labor arrest during first stage (First-stage Caesarean)	6 (20.7%)	10 (40.0%)	
Labor arrest during second stage (Second-stage Caesarean)	4 (13.8%)	5 (20.0%)	
Fetal hand prolapse	1 (3.4%)	0 (0.0%)	

chi^2 — the chi-squared test; df — degrees of freedom; F — the exact Fisher's test

Table 3. Postpartum complications among study participants

	Misoprostol [n = 93]	Dinoprostone [n = 108]	Dinoprostone + misoprostol [n = 39]	Significance
Any complication	14 (15.1%)	12 (11.1%)	9 (23.1%)	df = 2 $p^{chi2} = 0.196$
Blood transfusion	2 (2.2%)	2 (1.9%)	2 (5.1%)	$p^{F} = 0.470$
Uterine hyper-stimulation	2 (2.2%)	0	2 (5.1%)	$p^{F} = 0.059$
Curettage after delivery	8 (8.6%)	9 (8.3%)	3 (7.7%)	$p^{F} = 0.999$
Episiotomy	26 (28.0%)	42 (38.9%)	17 (43.6%)	df = 1 $p^{chi2} = 0.137$
Rupture of perineum (any type)	15 (16.1%)	24 (22.2%)	4 (10.3%)	df = 1 $p^{chi2} = 0.224$
Rupture of perineum No rupture I-stage II-stage III-stage	 78 (83.9%) 14 (15.1%) 1 (1.1%) 0	 84 (77.8%) 20 (18.5%) 2 (1.9%) 2 (1.9%)	 35 (89.7%) 3 (7.7%) 0 1 (2.6%)	$p^{F} = 0.427$

chi^2 — the chi-squared test; df — degrees of freedom; F — the exact Fisher's test

tracing or lack of the labour progress, although there was significantly more often emergency Caesarean delivery out of all deliveries ($p = 0.028$) in the misoprostol group (Tab. 2). For the analysis of the safety, the three groups, *i.e.*, misoprostol, dinoprostone and dinoprostone followed by misoprostol were considered. Delivery complications were categorized into the following: anaemia with blood transfusion need, uterine hyperstimulation, uterus curettage after delivery, shoulder dystocia or the perineum rupture needing surgical suturing. There were no significant differences in postpartum complications between groups (Tab. 3).

The oxytocin usage to accelerate the contraction activity of the uterine muscle was necessary in eight patients (8.6%) from the misoprostol group, and in 55 patients (37.4%) from dinoprostone group, which reached a statistically significant difference ($p < 0.001$).

The misoprostol use appeared to significantly shorten the time to any delivery compared to dinoprostone gel (medians: 14.5 vs 35.6 h, $p < 0.001$), it also shortened the time to beginning of delivery and vaginal delivery. There were no significant differences found in duration of any stage of labour between the two groups (Tab. 4).

There were statistically significant differences in Apgar scores of the baby (Tab. 5). The birth weight and length were statistically different, which may reflect the previously noted difference in gestational age at the delivery (Tab. 1 and 5).

As a next step, we checked whether woman's age had been associated with the analyzed time periods. After the

Table 4. Time intervals to delivery intention to treat groups

	Misoprostol first [n = 93]	Dinoprostone first [n = 147]	Significance
Time admission to delivery (vaginal or Caesarean section) [h] Mean, (SD) Median (Q1–Q3)	 47.0 (69.3)* 25.8 (14.0–44.0)	 67.3 (73.0)* 51.2 (31.3–81.3)	$p^{MW} < 0.001$
Time drug application to delivery (vaginal or Caesarean section) [h] Mean, (SD) Median (Q1–Q3)	 14.5 (13.8)* 11.0 (8.0–17.4)	 35.6 (25.0)* 28.8 (13.5–51.9)	$p^{MW} < 0.001$
Time drug application to vaginal delivery (Caesarean sections excluded) [h] Mean, (SD) Median (Q1–Q3)	[n = 64] 15.1 (15.6)* 11.0 (8.7–17.8)	[n = 107] 31.3 (24.4)* 26.0 (12.0–47.2)	$p^{MW} < 0.001$
Time drug application to the beginning of a labor [h] Mean, (SD) Median (Q1–Q3)	[n = 68] 9.9 (15.0)* 6.2 (3.9–11.5)	[n = 115] 25.3 (23.0)* 20.9 (5.8–40.8)	$p^{MW} < 0.001$
I stage of labor duration [h] Mean, (SD) Median (Q1–Q3)	[n = 68] 4.8 (2.2)* 4.8 (3.0–6.0)	[n = 115] 5.4 (2.7)* 5.0 (3.0–7.0)	$p^{MW} = 0.181$
II stage of labor duration [min] Mean, (SD) Median (Q1–Q3)	[n = 68] 30.0 (28.6)* 20.0 (10.0–40.0)	[n = 111] 37.7 (33.4)* 30.0 (15.0–60.0)	$p^{MW} = 0.058$
III stage of labor duration [min] Mean, (SD) Median (Q1–Q3)	[n = 63] 8.8 (5.6)* 10.0 (5.0–10.0)	[n = 106] 8.6 (4.2)* 10.0 (5.0–10.0)	$p^{MW} = 0.771$

*p < 0.05 by the Shapiro-Wilk test for normal distribution; MW — the U-Mann-Whitney test

Table 5. Neonatal outcomes across intention to treat misoprostol and dinoprostone groups

	Misoprostol first [n = 93]	Dinoprostone first [n = 147]	Significance
Apgar score [points] Mean, (SD) Median (Q1–Q3)	 9.4 (1.6)* 10.0 (10.0–10.0)	 9.8 (0.6)* 10.0 (10.0–10.0)	$p^{MW} = 0.041$
Apgar score ≤ 6 points at the 1st min (n, %) Apgar score 7–8 points at the 1st min (n, %) Apgar score 9–10 points at the 1st min (n, %)	8 (8.6%) 4 (4.3%) 81 (87.1%)	2 (1.4%) 4 (2.7%) 141 (95.9%)	$p^{F} = 0.018$
Birth weight [g] Mean, (SD) Median (Q1–Q3)	[n = 93] 3385 (530) 3420 (3045–3750)	[n = 146] 3623 (417) 3625 (3320–3955)	$p^{t-ue} < 0.001$
Birth length [cm] Mean, (SD) Median (Q1–Q3)	[n = 93] 54.9 (3.4) 55.0 (53.0–57.0)	[n = 146] 56.0 (3.0)* 56.0 (54.0–58.0)	$p^{MW} = 0.008$
Female [n, %]	44 (47.3%)	68 (46.3%)	df = 1 $p^{chi2} = 0.895$

*p < 0.05 by the Shapiro-Wilk test for normal distribution; MW — the U-Mann-Whitney test; t-ue — the Student's t-test for unequal variances

woman's age was regressed on the time from the drug implementation to the beginning of a labour (to the first stage of labour), to the delivery of a baby (to the end of second stage of labour) and additionally on the duration of the second stage of a labour only, no one result was statistically significant (p values: 0.114; 0.308; 0.131, respectively). Additionally, when the differences in the considered time periods between drug types were analysed with interaction terms between woman's age categorical variable no result had been significant either (p values: 0.970; 0.757; 0.800).

Finally, Cox regression models were performed to assess whether there were differences between misoprostol and dinoprostone upon time in the labour induction. The results showed that misoprostol increased more than twice the chance of beginning the labour or delivery of a baby in comparison to dinoprostone. Even after adjustment for the covariates which might influence the process, like mother's age, number of pregnancies, cervical state, and oxytocin use, the probability still was significantly higher (Tab. 6 and 7).

Table 6. The relative probability (assessed by the hazard ratio) for induction of a labor for misoprostol compared to dinoprostone

	Hazard ratio	95% CI	p value
Beginning of labor	2.57	1.85–3.57	p < 0.001
Beginning of labor[1]	2.44	1.75–3.40	p < 0.001
Beginning of labor[2]	2.42	1.73–3.39	p < 0.001
Beginning of labor[3]	2.10	1.49–2.97	p < 0.001

The proportional Cox regression model; [1]Adjusted for number of pregnancies, mother's age; [2]Adjusted for the covariates as in (1) and additionally for cervical effacement; [3]Adjusted for the covariates as in (2) and additionally for oxytocin use; CI — confidence interval

Table 7. The relative probability (assessed by the hazard ratio) for baby's delivery for misoprostol as compared to dinoprostone

	Hazard ratio	95% CI	p value
Baby's delivery	3.21	2.40–4.29	p < 0.001
Baby's delivery[1]	3.07	2.28–4.13	p < 0.001
Baby's delivery[2]	3.09	2.29–4.16	p < 0.001
Baby's delivery[3]	2.59	1.90–3.53	p < 0.001

The proportional Cox regression model; [1]Adjusted for number of pregnancies, mother's age; [2]Adjusted for the covariates as in (1) and additionally for cervical effacement; [3]Adjusted for the covariates as in (2) and additionally for oxytocin use; CI — confidence interval

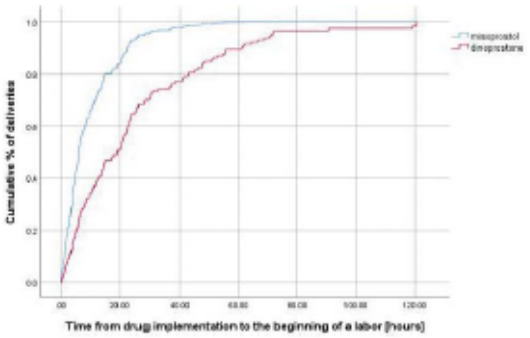

Figure 1. Cox regression model — from drug implementation to the beginning of labor

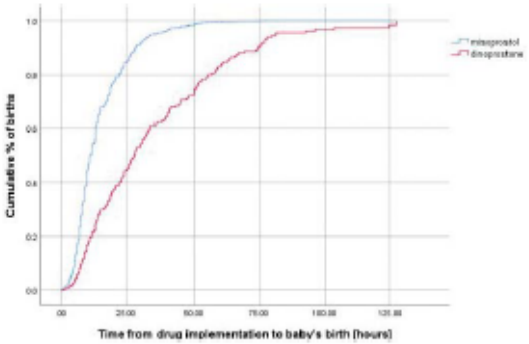

Figure 2. Cox regression model — from drug implementation to baby's delivery

DISCUSSION

The use of pharmaceutical induction of labour increased in many European countries during the last decades, for example in Norway the rate increased from 12.5% in 2003 to 20.3% in 2013. The rate of caesarean section in the induced patients' group did not change, and it remained stable at 17.1 and 17.4%, respectively [5]. It might be connected with introducing into the contemporary obstetrics the use of prostaglandins, which facilitate cervical ripening and accelerate uterine contractions like in the natural course of delivery.

The purpose of this study was a comparison of two prostaglandins used in everyday clinical practice, which are, among others, recommended by the Polish Society of Gynaecologists and Obstetricians Guidelines for labour induction [6]. We verified that vaginally implemented misoprostol insert was more effective than the dinoprostone gel in induction of labour in pregnant women without any comorbidities at term. Our findings are in line with the results of Sharp et al. [7] who demonstrated a statistically shorter time to the delivery when using misoprostol vaginal insert rather than dinoprostone vaginal gel, namely means 18.2 h (11.6–27.6) vs 21.8 h (19.0–23.9), respectively. In our study, the mean interval between the implementation of misoprostol to the time of delivery was even shorter (14.5 h). We have shown that misoprostol, in comparison to dinoprostone, resulted in twice higher chance of successful beginning of delivery regardless the number of previous pregnancies, gestational age or cervical state. Even if additionally, oxytocin use or mother's age were considered, the chance of labour initiation across time was still 1.9 times higher in this group (Tab. 6, Fig. 1). We observed similar effects on the time to baby's delivery (Tab. 7, Fig. 2). Those results indicated that misoprostol was more effective than dinoprostone in the induction of labour, which also further supported the findings of the other studies [8–9,12]. It is worth mentioning that most of available studies are based on different routes of administration of misoprostol (oral tablets, tablets implemented into the posterior vaginal fornix, vaginal insert) or dinoproston (vaginal insert, vaginal gel), which may interrupt the direct comparison between result and conclusions of those studies. One study which compared misoprostol vaginal insert (MVI) and misoprostol vaginal tablets (MVT) for induction of labour in term pregnancies [10] showed that MVI achieved a more vaginal delivery rate within 24-hours and shorter time from induction to vaginal delivery than MVT, with no influence on caesarean section rate, postpartum haemorrhage, Apgar score below 7. Remarkably similar conclusions were made after comparing of the misoprostol vaginal insert with oral misoprostol tablets in favour of vaginal rout [11].

The results of our study suggested that use of misoprostol vaginal insert shorten the time intervals from medicament implementation to active labour and to delivery itself when compared with preinduction with dinoprostone.

Incidence of vaginal deliveries after induction of labour vary widely in the literature; it was 92.5% [7], 88% [12], 73.3% [8] in the misoprostol group, compared with dinoprostone 89,1%, 74%, 71,6% respectively. In our study, the misoprostol intervention ended in the vaginal delivery in 68.8% cases in comparison to 76.9% in the dinoprostone group.

We observed lower mean birth weight of the neonates in the misoprostol group, which we assumed that was mostly connected with the lower gestational age in this group (40.6 vs 40.9 $p < 0.001$). However, we believe that it had no influence on the effectiveness of misoprostol, since there was another study where the misoprostol group had higher mean birth weight and gestational age compared to the dinoprostone group and the time interval to delivery was still shorter [12] or in another one in which the time from drug application to onset of labour was also significantly reduced [13].

As the prostaglandins' administration may result in many adverse outcomes, in both the mother and the infant, we analysed the results thoroughly. In both groups we have noticed disturbances in the foetal heart rate pattern described as foetal distress needing emergency caesarean delivery, with no statistical difference. In the end of our observation, we have shown that the caesarean delivery rates and its indications, as well as the maternal complications were not significantly different between studied groups.

In our study the analysis of the factors that potentially might have influenced the effect of each intervention showed no differences between the groups regarding maternal age, parity, prior vaginal delivery, miscarriage history, patients' body mass index, Bishop's scale score before the drug administration or estimated foetal weight.

There were a few limitations of this work that should be acknowledged. First, the study was retrospective and the enrolment of subjects for this study was not randomised. Additionally, we reviewed medical records as the source of information, and there were several missing data which were not possible to retrieve. Moreover, our sample size was limited; however, it was big enough to reach statistical significance for some of our results. It was not observed in our study any significant difference in the complication rate between different drugs, but, in our opinion, it should be confirmed on large sample size study. Thus, further studies on bigger groups are still needed.

CONCLUSIONS

Our study showed that using the misoprostol vaginal insert in comparison to dinoprostone gel seems to increase the chance of delivery and to shorten the time to beginning of the first stage of labour as well as the time to the delivery itself regardless the way, vaginal birth or caesarean section with no influence on maternal complications. Some lower Apgar scores observed in the misoprostol group requires further investigation.

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Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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Pregnancy-related comorbidities and labor induction — the effectiveness and safety of dinoprostone compared to misoprostol

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ABSTRACT

Objectives: The aim of the study was to evaluate whether the presence of the disease in pregnancy influences the effectiveness and safety of delivery preinduction with prostaglandins: misoprostol vaginal insert and dinoprostone vaginal gel.

Material and methods: This is a retrospective cohort study conducted of 560 pregnant women. The concomitant diseases mainly recorded were diabetes mellitus, hypertensive diseases, intrahepatic cholestasis of pregnancy, asthma, thrombocytopenia, and hypothyroidism. The primary study outcome was a successful vaginal delivery. The study above others evaluates the time from treatment implementation to the beginning of a labor and to a final delivery, the rate of Cesarean sections, and the presence of delivery complications.

Results: Among women with a concomitant disease, Caesarean section was observed more frequently in the misoprostol group. In the dinoprostone group, mothers with the concomitant disease as compared to healthy mothers required more time to the delivery and to achieve the beginning of labor. There were no differences in postpartum complications regardless of the prostaglandins, comorbidities or mothers' age. Neonates of mothers ≥ 35 years old with concomitant disease had lower average Apgar scores.

Conclusions: Our study showed that comorbidities seem to increase the caesarean section risk in the misoprostol preinduction group but in the dinoprostone group they prolong the time needed to achieve an active labour phase and a delivery.

Key words: comorbidities; dinoprostone; labor induction; misoprostol

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INTRODUCTION

In the era of postponing pregnancy to an advanced age of women, which has both social and economic determinants, various consequences of such decisions must be considered. Among older pregnant women, especially over 40 years old, the risk of comorbidities increases [1].

Hypertension in pregnancy concerns 6–10% of pregnancies [2, 3]. It is associated with numerous complications during pregnancy [4, 5]. The delivery beyond 37 weeks' gestation in pregnancies with the mild hypertensive disease was associated with improved maternal outcomes [6]. It has been proven, that labour induction at 38 or 39 weeks in pregnant women with uncomplicated chronic hypertension appears to reduce the risk of serious neonatal morbidity and mortality [7].

It is well known that diabetes type II is highly correlated with obesity and unfortunately obesity among women of reproductive age (20–39 years) increases, which altogether is concerning [8–9]. Obesity is a popular risk factor for stillbirth [10]. Fetal hypertrophy may lead to a disproportion of labour, shoulder dystocia during delivery, the need for urgent caesarean section with an increased risk of preoperative complications [11]. Both maternal gestational diabetes mellitus and obesity are independently associated with an unfavourable course of pregnancy and both have an even greater impact than either one alone [12]. In order

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to reduce the risk of fetal complications in pregnancy with pregestational diabetes and gestational diabetes, Polish Gynaecological Society recommends labour induction after 38 weeks and after 39 weeks of gestation, respectively [13].

Pregnant women older than 35 years have also increased risk of placenta previa, placental abruption or preterm birth and small-for-gestational age neonates. When comparing the adjusted perinatal mortality rates between women aged 20–24 with 35–39 and 40 years old, the rates were 63% ($p = 0.04$) and 183% ($p = 0.01$), respectively. Also, the rates of the adjusted perinatal mortality and morbidity rates were much higher in over 35 years-old pregnant group comparing with women under 25 years old [14]. There is the real risk of stillbirth in pregnant women aged 40 and more and that is why The Polish Society of Gynecologists and Obstetricians recommends to treat those pregnancies as biologically mature and to induct labour at 39 weeks of gestation [13].

As mentioned above there are studies showing the need for active rather than expectant management according to varies pregnancy complications and finishing the pregnancy before 40 weeks of gestation. The choice of the method, in accordance with the recommendations of The Polish Society of Gynecologists and Obstetricians, is based mainly on the assessment of obstetric state in each patient, the preferences of the deciding physician and, most often, the availability of a given procedure in a hospital.

The crucial role plays the maturity of the cervix mostly assessed by scale introduced by Bishop in 1964 [15]. There are many possible ways of preparing the cervix to the delivery which is called a labour pre-induction. The most often used ones include the mechanical ways (a Foley or a double-balloon catheter, membrane stripping) and the pharmacological way with the usage of prostaglandins in a numerous dosage and routs of administration (dinoprostone-prostaglandin E2 and misoprostol-prostaglandin E1) [16].

Available research results show effectiveness and safety of a use of prostaglandins for preinduction purposes, after a control for several covariates, and, as mentioned above, there are several clinical characteristics of the pregnant woman which are indications for the use of preinduction. The knowledge, however, on how the presence of a disease in pregnant woman influences clinical outcomes in those patients is very limited.

Objectives

The aim of the study was to evaluate whether the presence of the disease in pregnancy influences the effectiveness and safety of prostaglandins which are the most often used in routine clinical practice for preinduction, meaning: the misoprostol vaginal insert at a dose of 0.2 mg (Misodel, Ferring Pharmaceuticals Poland sp. z o.o) and dinoprostone gel at a dose of 0.5 mg (Prepidil, Pfizer Polska Sp. z o.o.). In details, the study assessed whether the presence of disease influences the effectiveness of the two aforementioned drugs measured by the time from treatment implementation to the beginning of a labour and to a final delivery and safety measured by the rate of emergency Caesarean sections, the presence of delivery complications, and some health indicators in newborns. Additionally, we addressed an issue of mothers' age as a potential contributing factor.

MATERIAL AND METHODS

The study included 560 pregnant women hospitalized at the Obstetric and Perinatology Department at the University Hospital in Cracow between January 2015 and April 2019. This was a retrospective cohort design for which all available medical records had been identified and reviewed. The list of collected information covered among others: maternal age, body mass index (BMI), number of pregnancies, parity history, gestational age. The mode of delivery, indications for caesarean section and other maternal outcomes including, episiotomy, anemia requiring blood transfusion, uterine hyperstimulation were also counted.

All patients identified as eligible for the study had to have singleton gestation with cephalic presentation and they required labour induction for medical indications. The cervical ripening was performed with dinoprostone gel or misoprostol insert. There were no known selection rules implemented by physicians at a clinic which might favor the use of one drug over the other due to patient's characteristics or preferences. Other inclusion criteria were the Bishop's score ≤ 4 and an absence of an active labour before administration of the drug. Exclusions included expected fetal weight over 4500 g or any known contraindication to vaginal delivery, or any contraindication for prostaglandins. For the presented study, pregnant women with any diagnosed disease were included. These were mainly: any tape of diabetes mellitus, hypertensive diseases, intrahepatic cholestasis of pregnancy, asthma and thrombocytopenia, hypothyroidism.

The primary study outcome was a successful vaginal delivery. Secondary effectiveness outcome measures were time from drug administration to delivery (both, vaginal and Caesarean section), induction-active labour interval time and durations of the first three delivery stages. The safety outcomes covered any complication observed during a labor such as blood transfusion, uterine hyperstimulation, curettage after delivery, episiotomy, rupture of perineum, and additionally emergency Caesarean delivery.

Statistical analysis

For the purpose of the study, all participants have been classified into two groups, a dinoprostone and

a misoprostol group. The categorization was made by the implementation of the intention to treat (ITT) principle. Thusly, mothers who were intended to begin their labour with dinoprostone and received dinoprostone as a first drug after admission were categorized as dinoprostone group members, and those who received misoprostol first composed a misoprostol group. There was also a group of women, in which, in the lack of effect of one drug, the other had been implemented. These were included according to the intention to treat (ITT) criteria in the appropriate group in the effectiveness analyses and additionally were analyzed as a separate group when complications were considered.

The descriptive characteristics of the investigated groups have been presented by the mean, SD, median and first (Q1) and third quartile (Q3). Median and quartiles were used as majority of data distributions were skewed causing the mean and SD were not informative enough to provide appropriate group depiction. To test whether there were differences in the study outcomes across analyzed groups the following strategy had been implemented for categorical data: 1. a chi-square test was used provided the expected values exceeded 5, otherwise, the Fisher's exact test was used; 2. to test whether there is a difference between mothers with a disease as compared to mothers without a disease across strata by mother's age (< 35 yrs vs 35 + yrs) the Cochran-Mantel-Haenszel statistics were used. This answered a question of whether the effect size caused by the presence of a disease across the two treatments differed between younger and older mothers. For continuous data: 1. firstly, the assumption of normal distribution had been tested using Shapiro-Wilk test; 2. as the variables analyzed were skewed the U-Mann-Whitney test was used to test for significance of a difference. The results with a $p < 0.05$ were considered statistically significant. The pairwise procedure was used for missing data, consequently all the available data were used for analyses. All analyses had been made by the IBM SPSS Statistics, version 26.

RESULTS

There were 560 women identified as admitted for a labour induction in the calendar period covered by the study. In this group, the misoprostol insert was applied to 210 pregnant women, and dinoprostone gel was used in 350 patients. In the dinoprostone group 100 women, who received additionally misoprostol as a second drug, were identified. In total, there were 320 women with at least one diagnosed disease 117 in the misoprostol and 203 in the dinoprostone group. Out of these 57 and 87, respectively, were diagnosed with hypothyroidism, 27 and 28 with hypertension, 23 and 65 had diabetes, 3 and 15 had both, diabetes and hypertension, and 7 and 8 had some other diseases. Women diagnosed with any concomitant disease had higher body mass and higher BMI in both dinoprostone and misoprostol groups. Women representing 35 + age category characterized a higher number of pregnancies. All the other characteristics were similar across analyzed groups (Tab. 1 and 2).

Among women with concomitant disease vaginal delivery was observed more frequently in the dinoprostone group as compared to misoprostol (66.5% vs 52.1%, $p = 0.013$). Consequently, Caesarean sections were observed more frequently in the misoprostol group. Moreover, mothers with a disease treated by misoprostol as compared to dinoprostone more frequently were referred to Caesarean section in emergency (Tab. 3). When we took into account the misoprostol group only, a higher proportion of pregnant women with a concomitant disease (as compared to women without the disease) underwent Caesarean section (47.9% vs 31.2%; $p = 0.016$), and also more of them experienced emergency Caesarean section (being a part out of total deliveries) (35.9% vs 20.4%; respectively, $p = 0.015$). Those differences were not observed in the dinoprostone group (Tab. 3). Some detailed analysis of Caesarean indications revealed that pregnant women with a disease treated by misoprostol more frequently presented preeclampsia and placenta abruption (both, when they were compared with mothers with a disease treated by dinoprostone, and with mothers treated by misoprostol but having no concomitant disease) (Tab. 3).

There were no differences in postpartum complications in the group of study participants regardless of the prostaglandin combination, any concomitant disease, or mothers' age, apart from more often need for episiotomy and an occurrence of rupture of perineum in dinoprostone group. (Tab. 4a and 4b).

Interesting findings are shown in Table 5 with time intervals from drug implementation to delivery (vaginal only or any delivery). It has been observed that in the group treated by dinoprostone, mothers with the concomitant disease as compared to mothers without the disease required more time to the delivery (vaginal route only: 39.6 vs 31.3 hours, $p = 0.014$, or any rout: 42.8 vs 35.6 hours, $p = 0.023$) and to achieve the beginning of a labor (33.5 vs 25.3, $p = 0.009$). After analysis of mothers' age, we have found no differences. In the misoprostol group, no significant differences in time intervals were found. The investigation of dinoprostone – misoprostol differences analyzed in the concomitant disease group we noticed that the time from the drug implementation to the onset of regular contraction activity of the uterus and to the delivery of the newborn was shorter for misoprostol as compared to dinoprostone and the differences were statistically significant (Tab. 5).

Table 1. Clinical characteristics of the study "ITT dinoprostone group" across study participants

	No concomitant disease			Any concomitant disease		
	Whole group [n = 147]	Mothers < 35 y [n = 119]	Mothers 35 + [n = 28]	Whole group [n = 203]	Mothers < 35 y [n = 164]	Mothers 35 + [n = 39]
Maternal age [years] Mean (SD) Median (Q1-Q3)	 30.4 (4.7) 30.0 (28.0–34.0)	 28.7 (3.5) 29.0 (27.0–31.0)	 37.4 (2.3) 37.0 (36.0–38.9)	 30.6 (4.4) 30.0 (28.0–33.0)	 29.1 (3.2) 29.0 (27.0–32.0)	 37.0 (2.1) 37.0 (35.0–38.0)
Weight at admission [kg] Mean (SD) Median (Q1-Q3)	[n = 83] 78.1 (12.6) 76.0 (69.0–85.0)	[n = 64] 77.9 (12.2) 74.9 (68.6–84.8)	[n = 19] 78.9 (14.2) 78.0 (70.0–88.0)	[n = 113] 81.3 (14.7) 79.0 (71.5–89.0)	[n = 90] 80.9 (15.1) 79.0 (70.8–89.0)	[n = 23] 82.7 (13.2) 80.0 (72.0–94.0)
Height [cm] Mean (SD) Median (Q1-Q3)	[n = 130] 167.2 (5.9) 168.0 (164.0– 171.0)	[n = 103] 167.9 (5.6) 168.0 (164.0–172.0)	[n = 27] 164.6 (6.6) 165.0 (160.0–170.0)	[n = 182] 165.6 (6.3) 165.0 (161.8–170.0)	[n = 147] 165.7 (6.3) 165.0 (162.0–170.0)	[n = 35] 164.9 (6.0) 165.0 (160.0–170.0)
Body mass index at admission [kg/m^2] Mean (SD) Median (Q1-Q3)	[n = 83] 27.7 (4.1) 27.1 (24.9–30.4)	[n = 64] 27.3 (3.7) 26.3 (24.7–29.3)	[n = 19] 29.4 (4.9) 30.1 (26.7–31.9)	[n = 113] 29.8 (4.8) 29.7 (25.9–32.1)	[n = 90] 29.6 (4.9) 29.7 (25.3–32.1)	[n = 23] 30.8 (4.4) 30.4 (27.7–33.3)
Number of pregnancies, n (%)						
1	97 (66.0%)	89 (74.8%)	8 (28.6%)	130 (64.0%)	113 (68.9%)	17 (43.6%)
2	27 (18.4%)	20 (16.8%)	7 (25.0%)	47 (23.2%)	37 (22.6%)	10 (25.6%)
≥ 3	23 (15.6%)	10 (8.4%)	13 (46.4%)	26 (12.8%)	14 (8.5%)	12 (30.8%)
Parity history (current delivery included), n (%)						
1	112 (76.2%)	99 (83.2%)	13 (46.4%)	155 (76.4%)	134 (81.7%)	21 (53.8%)
2	24 (16.3%)	17 (14.3%)	7 (25.0%)	34 (16.7%)	25 (15.2%)	9 (23.1%)
≥ 3	11 (7.5%)	3 (2.5%)	8 (28.6%)	14 (6.9%)	5 (3.0%)	9 (23.1%)
Nulliparous, n (%)	111 (75.5%)	100 (84.0%)	11 (39.3%)	151 (74.4%)	129 (78.7%)	22 (56.4%)
Miscarriage history, n (%)						
no	120 (81.6%)	103 (86.6%)	17 (60.7%)	169 (83.3%)	137 (83.5%)	32 (82.1%)
yes	27 (18.4%)	16 (13.4%)	11 (39.3%)	34 (16.7%)	27 (16.5%)	7 (17.9%)
Pre-ripening cervical characteristics, n (%)						
Dilatation ≤ 1 cm	138 (93.9%)	114 (95.8%)	24 (85.7%)	191 (94.1%)	154 (93.9%)	37 (94.9%)
Effacement ≤ 50%	140 (95.2%)	114 (95.8%)	26 (92.9%)	195 (96.1%)	157 (95.7%)	38 (97.4%)
Gestational age [weeks]# Mean (SD) Median (Q1-Q3)	 40.1 (1.0)* 40.0 (40.0–41.0)	 40.1 (1.0) 40.0 (40.0–41.0)	 40.1 (1.0) 40.0 (40.0–41.0)	 39.6 (1.4) 40.0 (39.0–41.0)	 39.6 (1.3) 40.0 (39.0–41.0)	 39.3 (1.6) 40.0 (38.0–40.0)
Estimated birth weight [g] Mean (SD) Median (Q1-Q3)	[n = 54] 3553.6 (49.8) 3615.5 (3241.3–3868.8)	[n = 48] 3554.6 (416.3) 3607.5 (3257.5–3874.3)	[n = 6] 3545.7 (388.6) 3653.0 (3115.0–3875.0)	[n = 54] 3529.2 (514.6) 3662.5 (3300.0–3862.5)	[n = 47] 3536.7 (510.2) 3671.0 (3358.0–3855.0)	[n = 7] 3478.1 (583.0) 3300.0 (3262.0–3975.0)

*$p < 0.05$ by the Shapiro-Wilk test for normal distribution; #at a time of administration of the first dose of the drug

Interestingly, there were no significant differences observed between investigated drugs in the duration of the 1st, 2nd, and 3rd stage of labor. The effect of age was noticed in the dinoprostone group only (Tab. 5).

Finally, neonatal outcomes were analyzed. In the Apgar score analyses the only statistically significant difference was found in the group of mothers with a disease treated by misoprostol, as in this group older (35 +) mothers delivered babies with lower Apgar scores on average (9.0 vs 9.7 pts, $p < 0.001$) and additionally, significantly higher proportion of babies with a score of ≤ 6 (7.4% vs 2.2%) and Apgar 7–8 (22.2% vs 3.3%) was observed (Tab. 6).

DISCUSSION

The comorbidities in a pregnant woman, like hypertension, diabetes mellitus, alloimmune disease, intrahepatic cholestasis or renal disease, may be a serious medical conditions influencing a wellbeing of a woman and her baby. The states mentioned are often indications for a labour induction. The several national obstetrical associations have established recommendations for most common diseases pointing out the need of the elective and active management before the due date at 40 weeks of gestation in order to reduce the perinatal and maternal risk [13,17–19]. There is still an open question, however, about the best (the saf-

Table 2. Clinical characteristics of the study "ITT misoprostol group" across study participants

	No concomitant disease			Any concomitant disease		
	Whole group [n = 93]	**Mothers < 35 y [n = 73]**	**Mothers 35 + [n = 20]**	**Whole group [n = 117]**	**Mothers < 35 y [n = 90]**	**Mothers 35 + [n = 27]**
Maternal age [years] Mean (SD) Median (Q1-Q3)	 31.1 (4.4)* 31.0 (28.5–34.0)	 29.5 (3.4) 30.0 (28.0–32.0)	 36.8 (2.5) 36.0 (35.0–38.0)	 30.8 (4.0) 31.0 (28.0–34.0)	 29.2 (3.0) 29.0 (27.0–31.3)	 36.1 (1.4) 36.0 (35.0–37.0)
Weight at admission [kg] Mean (SD) Median (Q1-Q3)	[n = 47]* 76.8 (10.9) 75.0 (69.0–83.0)	[n = 34] 76.6 (10.9) 75.0 (68.8–83.0)	[n = 13] 77.4 (11.4) 73.0 (70.0–84.5)	[n = 66] 84.2 (16.2) 83.0 (71.5–93.3)	[n = 46] 86.6 (16.5) 85.0 (75.8–94.5)	[n = 20] 78.6 (14.2) 77.0 (70.0–88.5)
Height [cm] Mean (SD) Median (Q1-Q3)	[n = 84] 165.7 (5.7) 166.5 (162.0–170.0)	[n = 68] 166.2 (5.6) 167.0 (163.0–170.0)	[n = 16] 163.4 (5.6) 164.5 (158.5–167.8)	[n = 110] 166.9 (5.7) 167.0 (163.8–170.0)	[n = 83] 166.9 (6.1) 167.0 (162.0–170.0)	 167.0 (4.3) 168.0 (164.0–170.0)
Body mass index at admission [kg/m^2] Mean (SD) Median (Q1-Q3)	 [n = 46] 28.5 (3.7)* 27.4 (25.9–30.4)	 [n = 34] 28.1 (3.4) 27.3 (25.7–29.8)	 [n = 12] 29.7 (4.2) 29.3 (26.1–31.7)	 [n = 66] 30.2 (5.4) 29.9 (25.9–33.4)	 [n = 46] 31.0 (5.5) 30.5 (27.3–33.8)	 [n = 20] 28.4 (4.6) 27.6 (24.6–31.8)
Number of pregnancies, n (%)						
1	52 (55.9%)	45 (61.6%)	7 (35.5%)	74 (63.2%)	58 (64.4%)	16 (59.3%)
2	20 (21.5%)	16 (21.9%)	4 (20.0%)	23 (19.7%)	17 (18.9%)	6 (22.2%)
≥ 3	21 (22.6%)	12 (16.4%)	9 (45.0%)	20 (17.1%)	15 (16.7%)	5 (18.5%)
Parity history (current delivery included), n (%)						
1	64 (68.8%)	54 (74.0%)	10 (50.0%)	95 (81.2%)	75 (83.3%)	20 (74.1%)
2	18 (19.4%)	14 (19.2%)	4 (20.0%)	17 (14.5%)	12 (13.3%)	5 (18.5%)
≥ 3	11 (11.8%)	5 (6.8%)	6 (30.0%)	5 (4.3%)	3 (3.3%)	2 (7.4%)
Nulliparous, n (%)	62 (66.7%)	53 (72.6%)	9 (45.0%)	88 (75.2%)	70 (77.8%)	18 (66.7%)
Miscarriage history (n, %)						
no	70 (75.3%)	57 (78.1%)	13 (65.0%)	89 (76.1%)	67 (74.4%)	22 (81.5%)
yes	23 (24.7%)	16 (21.9%)	7 (35.0%)	28 (23.9%)	23 (25.6%)	5 (18.5%)
Pre-ripening cervical characteristics, n (%)						
Dilatation ≤ 1 cm	86 (92.5%)	69 (94.5%)	17 (85.0%)	108 (92.3%)	83 (92.2%)	25 (92.6%)
Effacement ≤ 50%	85 (91.4%)	67 (91.8%)	18 (90.0%)	112 (95.7%)	85 (94.4%)	27 (100.0%)
Gestational age [weeks]# Mean (SD) Median (Q1-Q3)	 39.7 (1.8)* 40.6 (38.9–40.9)	 39.4 (1.8) 40.0 (39.0–41.0)	 38.9 (1.8) 40.0 (37.3–40.0)	 38.9 (2.0) 40.0 (38.0–40.0)	 39.0 (2.0) 40.0 (38.0–40.0)	 38.6 (2.0) 39.0 (38.0– 40.0)
Estimated birth weight [g] Mean (SD) Median (Q1-Q3)	[n = 54] 3325.0 (552.1)* 3450.0 (3000.0–3747.8)	[n = 43] 3375.4 (513.2) 3456.0 (3075.0–3800.0)	[n = 11] 3127.9 (675.1) 3250.0 (2800.0–3500.0)	[n = 59] 3288.5 (608.6) 3400.0 (2922.0–3786.0)	[n = 49] 3302.0 (576.3) 3400.0 (2939.0–3758.0)	 3222.4 (780.7) 3414.5 (2446.3–3850.0)

*$p < 0.05$ by the Shapiro-Wilk test for normal distribution; #at a time of administration of the first dose of the drug

est, and effectively leading to vaginal birth) way of a labour induction in a specific clinical situation. Several of observational studies have suggested that induction of labour at term is associated with reduction of perinatal mortality and morbidity and maternal complications [20] without increasing the Caesarean rate risk [21–22].

In our investigation we tried to reveal whether one of the two prostaglandins, dinoprostone or misoprostol, preponderate the other considering effectiveness and safety in high-risk pregnancy. Our study showed statistically important differences in Caesarean section rate and time intervals from drug implementation to delivery between groups. Our findings, however, are difficult to compare with other results, as, by our knowledge, there are no such studies published. The study investigated pregnancies with different kinds of complications presented that misoprostol usage in a group of small-for-gestational age neonates at delivery was not associated with an increased risk of Caesarean section when compared with dinoprostone or Foley catheter preinduction. The authors concluded then, that all investigated cervical ripening agents had similar efficacy and safety in small-for-gestational age pregnancies which is not in consistence with our results [23]. On the other hand, literature data indicate an increased risk of Caesarean sec-

Table 3. Mode of delivery and indications for caesarean section across drug and the presence of concomitant disease (ITT groups)

	Dinoprostone				Misoprostol				p value for dinoprostone vs misoprostol in 'any concomitant disease' group
	No concomitant disease [n = 147]	Any concomitant disease [n = 203]	No disease vs any concomitant disease		No concomitant disease [n = 93]	Any concomitant disease [n = 117]	No disease vs any concomitant disease		
			Mothers < 35 y [283]	Mothers 35 + [n = 67]			Mothers < 35 y [n = 163]	Mothers 35 + [n = 47]	
Caesarean section	27.2%	33.5%	25.2% vs 32.9%	35.7% vs 35.9%	31.2%	47.9%	27.4% vs 42.2%	45.0% vs 66.7%	$p^{chi2} = 0.013$
	$p^{chi2} = 0.241$		$p^{MH} = 0.256$		$p^{chi2} = 0.016$		$p^{MH} = 0.022$		
Emergency Caesarean delivery out of total deliveries	12.2%	14.8%	11.8% vs 14.6%	14.3% vs 15.4%	20.4%	35.9%	15.1% vs 31.1%	40.0% vs 51.9%	$p^{chi2} < 0.001$
	$p^{chi2} = 0.532$		$p^{MH} = 0.256$		$p^{chi2} = 0.015$		$p^{MH} = 0.022$		
Emergency Caesarean delivery out of total Caesarean sections	[n = 40] 45.0%	[n = 68] 44.1%	[n = 30 vs 54] 46.7% vs 44.4%	[n = 10 vs 14] 40.0% vs 42.9%	[n = 29] 65.5%	[n = 56] 75.0%	[n = 20 vs 38] 55.0% vs 73.7%	[n = 9 vs 18] 88.9% vs 77.8%	$p^{chi2} < 0.001$
	$p^{chi2} = 0.999$		$p^{MH} = 0.925$		$p^{chi2} = 0.447$		$p^{MH} = 0.515$		
Vaginal delivery	72.8%	66.5%	74.8% vs 67.1%	64.3% vs 64.1%	68.8%	52.1%	72.6% vs 57.8%	55.0% vs 33.3%	$p^{chi2} = 0.013$
	$p^{chi2} = 0.241$		$p^{MH} = 0.256$		$p^{chi2} = 0.016$		$p^{MH} = 0.022$		
Indications for Caesarean section	[n = 40]	[n = 68]	[n = 30 vs 54]	[n = 10 vs 14]	[n = 29]	[n = 56]	[n = 20 vs 38]	[n = 9 vs 18]	
• Foetal distress	45.0%	36.8%	46.7% vs 38.9%	40.0% vs 28.6%	62.1%	62.5%	50.0% vs 57.9%	88.9% vs 72.2%	
• Preeclampsia	–	–	–	–	0%	3.6%	0% vs 2.6%	0% vs 5.6%	
• Placenta abruption	0%	7.4%	0% vs 5.6%	0% vs 14.3%	0%	8.9%	0% vs 13.2%	–	
• Labour arrest during first stage (First-stage Caesarean)	40.0%	48.5%	40.0% vs 48.1%	40.0% vs 50.0%	20.7%	25.0%	25.0% vs 26.3%	11.1% vs 22.2%	
• Labour arrest during second stage (Second-stage Caesarean)	15.0%	7.4%	13.3% vs 7.4%	20.0% vs 7.1%	4 (13.8%)	0 (0%)	20.0% vs 0%	–	
• Fetal hand prolapse	–	–	–	–	3.4%	0%	5.0% vs 0%	–	
	$p^{F} = 0.161$		#		$p^{F} = 0.015$		#		$p^{F} = 0.002$

chi2 — the chi-squared test with 1 degree of freedom; F — the exact Fisher's test; # — due to no data in all contingency tables the p-value for the common odds ratio has not been estimated; MH — the Cochran-Mantel-Haenszel statistics

Table 4a. Postpartum complications among study participants (ITT groups)

	Dinoprostone				Misoprostol				p value for dinoprostone vs misoprostol in 'any concomitant disease' group
	No concomitant disease [n = 147]	Any concomitant disease [n = 203]	No disease vs any concomitant disease		No concomitant disease [n = 93]	Any concomitant disease [n = 117]	No disease vs any concomitant disease		
			Mothers < 35y [283]	Mothers 35 + [n = 67]			Mothers < 35y [n = 163]	Mothers 35 + [n = 47]	
Any complication	14.3%	10.8%	11.8% vs 11.0%	25.0% vs 10.3%	15.1%	9.4%	12.3% vs 6.7%	25.0% vs 18.5%	
	$p^{chi2} = 0.410$		$p^{MH} = 0.420$		$p^{chi2} = 0.283$		$p^{MH} = 0.275$		$p^{chi2} = 0.709$
Blood transfusion	2.7%	2.5%	1.7% vs 2.4%	7.1% vs 2.6%	2.2%	0.9%	2.7% vs 0%	0% vs 3.7%	
	$p^{F} = 0.999$		$p^{MH} = 0.850$		$p^{F} = 0.585$		$p^{MH} = 0.835$		$p^{F} = 0.421$
Uterine hyper-stimulation	1.4%	0%	0.8% vs 0%	3.6% vs 0%	2.2%	0.9%	2.7% vs 1.1%	0% vs 0%	
	$p^{F} = 0.176$		$p^{MH} = 0.343$		$p^{F} = 0.585$		$p^{MH} = 0.855$		$p^{F} = 0.366$
Curettage after delivery	8.2%	7.9%	8.4% vs 8.5%	7.1% vs 5.1%	8.6%	3.4%	6.8% vs 2.2%	15.0% vs 7.4%	
	$p^{chi2} = 0.999$		$p^{MH} = 0.916$		$p^{chi2} = 0.138$		$p^{MH} = 0.180$		$p^{chi2} = 0.151$
Episiotomy	40.1%	40.4%	45.4% vs 44.5%	17.9% vs 23.1%	28.0%	27.4%	32.9% vs 28.9%	10.0% vs 22.2%	
	$p^{chi2} = 0.999$		$p^{MH} = 0.956$		$p^{chi2} = 0.999$		$p^{MH} = 0.926$		$p^{chi2} = 0.021$
Rupture of perineum (any type)	19.0%	13.3%	16.8% vs 12.2%	28.6% vs 17.9%	16.1%	12.0%	17.8% vs 13.3%	10.0% vs 7.4%	
	$p^{chi2} = 0.180$		$p^{MH} = 0.189$		$p^{chi2} = 0.425$		$p^{MH} = 0.519$		$p^{chi2} = 0.862$
Rupture of perineum									
• No rupture	81.0%	86.7%	83.2% vs 87.8%	71.4% vs 82.1%	83.9	88.0%	82.2% vs 86.7%	90.0% vs 92.6%	
• I-stage	15.6%	12.3%	13.4% vs 11.0%	25.0% 17.9%	15.1%	6.8%	16.4% vs 7.8%	10.0% vs 3.7%	
• II-stage	1.4%	1.0%	1.7% vs 1.2%	0% vs 0%	1.1%	3.4%	1.4% vs 4.4%	0% vs 0%	
• III-stage	2.0%	0%	1.7% vs 0%	3.6% vs 0%	0%	1.7%	0% vs 1.1%	0% vs 3.7%	
	$p^{F} = 0.149$		#		$p^{F} = 0.093$		#		$p^{F} = 0.036$

chi2 — the chi-squared test with 1 degree of freedom; F — the exact Fisher's test; # — due to no data in all contingency tables the p-value for the common odds ratio has not been estimated; MH — the Cochran-Mantel-Haenszel statistics

Table 4b. Postpartum complications among study participants in the group receiving both drugs (i.e. dinoprostone and misoprostol)

	Dinoprostone followed by misoprostol			
	No concomitant disease [n = 39]	Any concomitant disease [n = 61]	No disease vs any concomitant disease	
			Mothers < 35 y [n = 89]	Mothers 35 + [n = 11]
Any complication	23.1%	16.4%	15.2% vs 14.3%	66.7% vs 40.0%
	$p^{chi2} = 0.282$		$p^{MH} = 0.824$	
Blood transfusion	5.1%	4.9%	3.0% vs 3.6%	16.7% vs 20.0%
	$P^{F}=0.999$		$p^{MH}=0.780$	
Uterine hyper-stimulation	5.1%	0%	3.0% vs 0%	16.7% vs 0%
	$P^{F} = 0.150$		$p^{MH} = 0.400$	
Curettage after delivery	7.7%	9.8%	9.1% vs 10.7%	0% vs 0%
	$P^{F} = 0.999$		$p^{MH} = 0.906$	
Episiotomy	43.6%	37.7%	48.5% vs 41.1%	16.7% vs 0%
	$p^{chi2} = 0.676$		$p^{MH} = 0.521$	
Rupture of perineum (any type)	10.3%	14.8%	9.1% vs 14.3%	16.7% vs 20.0%
	$p^{chi2} = 0.561$		$p^{MH} = 0.$	
Rupture of perineum				
No rupture	89.7%	85.2%	90.9% vs 85.7%	83.3% vs 80.0%
I-stage	7.7%	13.1%	9.1% vs 12.5%	0% vs 20.0%
II-stage	0%	1.6%	0% vs 1.8%	0% vs 0%
III-stage	2.6%	0%	0% vs 0%	16.7% vs 0%
	$P^{F} = 0.471$		#	

chi2 — the chi-squared test with 1 degree of freedom; F — the exact Fisher's test; # — due to no data in all contingency tables the p-value for the common odds ratio has not been estimated; MH — the Cochran-Mantel-Haenszel statistics

tion in women with pre-eclampsia in the dinoprostone induced labour group, regardless of the number of deliveries and gestational age, but no differences were found in the group with hypertension without pre-eclampsia and in the group without hypertensive diseases at all [24]. This is in conformity with our data showing no differences according to presence of concomitant disease in dinoprostone group. There were also no differences in the risk of Caesarean section, depending on the gestational age in the dinoprostone induced group of women with gestational hypertension [25]. In view of these results, we speculate that the higher rate of Caesarean rate in the misoprostol group might be related to the comorbidity of pregnant women with no such effect in the dinoprostone group.

No differences were found in perinatal outcomes when misoprostol was used in the groups with and without hypertensive diseases [26] as well as the dinoprostone insert did not adversely affect the perinatal outcomes compared to the group of women with spontaneous or oxytocin-stimulated delivery in the group of women with hypertension [27]. In our study, only babies in the subgroup of mothers over 35 years old with any concomitant disease had statistically significant lower average Apgar scores comparing with younger mothers with comorbidities. These findings require more detailed analyses on larger study groups. Regarding the neonatal safety of a preinduction of a labour in a pregnancy with any comorbidity, because only the Apgar points at the first minute were assessed, we cannot draw a definite conclusion. Nevertheless, the data we have gained show no differences in Apgar score between dinoprostone and misoprostol in any concomitant disease groups.

In our study we did not find significant differences in postpartum complications among pregnant women with any concomitant disease after labour induction using either dinoprostone or misoprostol, what is similar to other retrospective study concerning the induction of labour in hypertensive and normotensive patients with misoprostol and dinoprostone vaginal inserts. The authors also showed no differences in time to achieve active labour or to overall delivery when considering such confounding variables as BMI, gestational age, Bishop's scale or the time from drug administration to the active phase of labour [28]. Nevertheless, they showed that women with hypertension need more time to achieve active labour or overall delivery both in misoprostol and dinoprostone groups. Similarly, it has been proven that pregnant women with diabetes need more time to maturation of the cervix measured by the Bishop scale and simply need a longer time to reach the active stage of

Table 5. Time intervals to delivery across drug and the presence of concomitant disease (ITT groups)

	Dinoprostone				Misoprostol				p value for dinoprostone vs misoprostol in 'any concomitant disease' group
	No concomitant disease [n = 147]	Any concomitant disease [n = 203]	Any concomitant disease		No concomitant disease [n = 93]	Any concomitant disease [n = 117]	Any concomitant disease		
			Mothers < 35y [n = 164]	Mothers 35 + [n = 39]			Mothers < 35y [n = 90]	Mothers 35 + [n = 27]	
Time admission to delivery (vaginal or Caesarean section) [h]	67.3 (73.0)*	88.1 (95.1)*	92.9 (102.0)*	67.6 (54.2)*	47.0 (69.3)*	62.1 (133.0)*	61.4 (145.0)*	64.6 (83.4)*	
Mean, (SD)	51.2 (31.3–81.3)	63.4 (35.5–97.8)	63.9 (35.5–103.4)	56.8 (32.3–82.3)	25.8 (14.0–44.0)	23.2 (13.9–45.8)	22.7 (14.0–45.4)	33.3 (12.7–82.5)	$p^{UMW} < 0.001$
Median (Q1–Q3)	$p^{UMW} = 0.007$		$p^{UMW} = 0.185$		$p^{UMW} = 0.896$		$p^{UMW} = 0.561$		
Time drug application to delivery (vaginal or Caesarean section) [h]	35.6 (25.0)*	42.8 (29.1)*	44.0 (30.4)*	37.7 (22.8)	14.5 (13.8)*	12.9 (8.3)*	12.9 (8.3)*	12.9 (8.4)*	
Mean, (SD)	28.8 (13.5–51.9)	36.0 (18.6–59.0)	36.9 (18.5–65.1)	35.0 (21.5–54.5)	11.0 (8.0–17.4)	11.0 (7.8–15.9)	11.0 (8.0–15.2)	10.5 (7.0– 16.8)	$p^{UMW} < 0.001$
Median (Q1–Q3)	$p^{UMW} = 0.023$		$p^{UMW} = 0.447$		$p^{UMW} = 0.445$		$p^{UMW} = 0.727$		
Time drug application to vaginal delivery (Caesarean sections excluded) [h]	[n = 107]	[n = 135]	[n = 110]	[n = 25]	[n = 64]	[n = 61]	[n = 52]	[n = 9]	
Mean, (SD)	31.3 (24.4)*	39.6 (28.6)*	40.7 (30.0)*	34.7 (21.1)	15.1 (15.6)*	12.7 (5.3)*	14.0 (12.7)*	13.0 (5.9)	
Median (Q1–Q3)	26.0 (12.0–47.2)	33.8 (15.7–54.0)	34.4 (16.0–54.2)	32.0 (15.2–51.9)	11.0 (8.7–17.8)	11.0 (9.0–15.0)	11.0 (9.0–14.4)	11.4 (7.8– 16.9)	$p^{UMW} < 0.001$
	$p^{UMW} = 0.014$		$p^{UMW} = 0.662$		$p^{UMW} = 0.942$		$p^{UMW} = 0.924$		
Time drug application to the beginning of a labour [h]	[n = 115]	[n = 144]	[n = 118]	[n = 26]	[n = 68]	[n = 61]	[n = 52]	[n = 9]	
Mean, (SD)	25.3 (23.0)*	33.5 (27.7)*	34.4 (29.1)*	29.7 (20.3)	9.9 (15.0)*	7.3 (5.4)*	7.2 (5.3)*	7.7 (6.1)	
Median (Q1–Q3)	20.9 (5.8–40.8)	27.2 (10.9–47.9)	27.2 (10.2–48.1)	25.3 (10.9–48.4)	6.2 (3.9–11.5)	5.8 (3.8–9.3)	5.8 (3.9–8.4)	5.7 (2.8–11.0)	$p^{UMW} < 0.001$
	$p^{UMW} = 0.009$		$p^{UMW} = 0.858$		$p^{UMW} = 0.425$		$p^{UMW} = 0.908$		
I stage of labour duration [h]	[n = 115]	[n = 144]	[n = 118]	[n = 26]	[n = 68]	[n = 61]	[n = 52]	[n = 9]	
Mean, (SD)	5.4 (2.7)*	5.2 (2.2)*	5.3 (2.2)*	4.4 (2.2)*	4.8 (2.2)*	4.8 (2.2)*	4.8 (2.3)*	4.8 (1.1)*	
Median (Q1–Q3)	5.0 (3.0–7.0)	5.0 (4.0–6.0)	5.0 (4.0–6.3)	4.0 (3.0–6.0)	4.8 (3.0–6.0)	4.0 (4.0–6.0)	4.0 (3.0–6.0)	4.0 (4.0–5.8)	$p^{UMW} = 0.192$
	$p^{UMW} = 0.796$		$p^{UMW} = 0.025$		$p^{UMW} = 0.991$		$p^{UMW} = 0.530$		
II stage of labour duration] min]	[n = 111]	[n = 133]	[n = 110]	[n = 25]	[n = 68]	[n = 61]	[n = 52]	[n = 9]	
Mean, (SD)	37.7 (33.4)*	32.6 (28.2)*	33.1 (27.5)*	30.4 (31.3)*	30.0 (28.6)*	34.7 (31.6)*	33.8 (32.1)*	27.8 (29.1)*	
Median (Q1–Q3)	30.0 (15.0–60.0)	20.0 (10.0–45.0)	20.0 (15.0–45.0)	15.0 (7.5–45.0)	20.0 (10.0–40.0)	25.0 (10.0–47.0)	30.0 (10.0–54.8)	15.0 (12.5–35.0)	$p^{UMW} = 0.791$
	$p^{UMW} = 0.246$		$p^{UMW} = 0.221$		$p^{UMW} = 0.266$		$p^{UMW} = 0.483$		
III stage of labour duration [min]	[n = 106]	[n = 127]	[n = 104]	[n=23]	[n = 63]	[n = 60]	[n = 51]	[n = 9]	
Mean, (SD)	8.6 (4.2)*	8.9 (4.9)*	9.1 (5.1)*	8.0 (3.6)*	8.8 (5.6)*	9.3 (4.8)*	9.0 (4.2)*	11.1 (7.4)*	
Median (Q1–Q3)	10.0 (5.0–10.0)	10.0 (5.0–10.0)	10.0 (5.0–10.0)	10.0 (5.0–10.0)	10.0 (5.0–10.0)	10.0 (5.0–10.0)	10.0 (5.0–10.0)	10.0 (7.5–10.0)	$p^{UMW} = 0.373$
	$p^{UMW} = 0.770$		$p^{UMW} = 0.383$		$p^{UMW} = 0.197$		$p^{UMW} = 0.450$		

*- $p < 0.05$ by the Shapiro-Wilk test for normal distribution; UMW — the U Mann-Whitney test

Table 6. Neonatal outcomes across drug and the presence of concomitant disease (ITT groups)

	Dinoprostone				Misoprostol				p value for dinoprostone vs misoprostol in 'any concomitant disease' group
	No concomitant disease [n = 147]	Any concomitant disease [n = 203]	Any concomitant disease		No concomitant disease [n = 93]	Any concomitant disease [n = 117]	Any concomitant disease		
			Mothers < 35y [n = 164]	Mothers 35 + [n = 39]			Mothers < 35y [n = 90]	Mothers 35 + [n = 27]	
Apgar score (points) Mean, (SD) Median (Q1–Q3)	9.8 (0.6)* 10.0 (10.0–10.0)	9.6 (1.1)* 10.0 (10.0–10.0)	10.0 (1.2)* 10.0 (10.0–10.0)	9.6 (0.9)* 10.0 (9.0–10.0)	9.4 (1.6)* 10.0 (10.0–10.0)	9.6 (1.1)* 10.0 (10.0–10.0)	9.7 (0.8)* 10.0 (10.0–10.0)	9.0 (1.5)* 10.0 (8.0–10.0)	$p^{UMW} = 0.216$
	$p^{UMW} = 0.164$		$p^{UMW} = 0.079$		$p^{UMW} = 0.883$		$p^{UMW} < 0.001$		
Apgar score ≤ 6 points at the 1st min (n, %)	1.4%	3.0%	3.7%	0%	8.6%	3.4%	2.2%	7.4%	
Apgar score 7-8 points at the 1st min (n, %)	2.7%	4.9%	3.7%	10.3%	4.3%	7.7%	3.3%	22.2%	
Apgar score 9–10 points at the 1st min (n, %)	95.9%	92.1%	92.6%	89.7%	87.1%	88.9%	94.4%	70.4%	
	$p^{F} = 0.368$		$p^{F} = 0.150$		$p^{chi2} = 0.175$		$p^{F} = 0.003$		$p^{F} = 0.548$
Birth weight [g] Mean, (SD) Median (Q1–Q3)	[n = 146] 3623 (417) 3625 (3320–3955)	3459 (450)* 3510 (3200–3760)	3470.5 (421.7)* 3515.0 (3202.5–3760.0)	3410.8 (556.5) 3510.0 (3110.0–3800.0)	3385 (530) 3420 (3045–3750)	3293 (565)* 3330 (2970–3700)	3304.2 (543.3)* 3335.0 (3032.5–3682.5)	3256.3 (643.1) 3250.0 (2750.0–3388.0)	$p^{UMW} = 0.011$
	$p^{UMW} = 0.001$		$p^{UMW} = 0.898$		$p^{UMW} = 0.305$		$p^{UMW} = 0.764$		
Birth length [cm] Mean, (SD) Median (Q1–Q3)	[n = 146] 56.0 (3.0)* 56.0 (54.0–58.0)	55.2 (2.9)* 56.0 (53.0–57.0)	55.2 (2.7)* 56.0 (53.0–57.0)	55.2 (3.6) 55.0 (53.0–57.0)	54.9 (3.4) 55.0 (53.0–57.0)	54.4 (3.3)* 55.0 (53.0–57.0)	54.6 (3.4)* 55.0 (53.0–57.0)	53.9 (3.0) 54.0 (52.0–56.0)	$p^{UMW} = 0.050$
	$p^{UMW} = 0.008$		$p^{UMW} = 0.880$		$p^{UMW} = 0.372$		$p^{UMW} = 0.302$		
Female (n, %)	46.3%	49.8%	48.8%	53.8%	47.3%	55.6%	51/1%	70.4%	$p^{chi2} = 0.353$
	$p^{chi2} = 0.588$		$p^{chi2} = 0.597$		$p^{chi2} = 0.267$		$p^{chi2} = 0.121$		

* - $p < 0.05$ by the Shapiro-Wilk test for normal distribution; UMW — the U Mann-Whitney test; ^{chi2} — the chi-squared test with 1 degree of freedom; F — the exact Fisher's test; # — due to no data in all contingency tables the p-value for the common odds ratio has not been estimated

a labor, but without differences in its duration. The study also showed that women with diabetes needed a statistically significant longer time to give birth after administration of prostaglandins when compared to women without diabetes regardless the prostaglandin used [29]. Both cited studies are partially in agreement to our study showing pregnant women with any concomitant disease need statistically more time from drug application to the beginning of labour or to the delivery in dinoprostone preinduction group with the opposite, but not statistically important, observations in misoprostol group. The present analysis of women with comorbidities undergoing labour preinduction using misoprostol vaginal inserts showed strong statistical differences in time intervals from drug implementation to active phase achievement and to delivery when comparing with dinoprostone gel. That may lead to the conclusion of obtaining a faster effect of misoprostol used in the group of pregnant women with concomitant diseases.

Our study has several strengths, as the access to the data enables us to analyze a fair number of pregnant women, which increases the power of the study, the analysis of clinical data using cohort retrospective design provided an opportunity to assess effectiveness rather than efficacy, but in that way provided information on how the investigated treatments lead to the effect in real clinical practice. Next, we were able to analyze the clinical features of mothers and her babies which provided information on safety. An additional benefit is the ability to analyze the effects across the mother's age categories.

The provided results however are not free from some limitations, as mothers with a disease were investigated as one group, but the group was represented by different comorbidities. Primarily, we believed, that our investigation would be able to answer whether there is an effect of concomitant diabetes or hypertension in pregnancy on the pregnancy outcomes if labour induction took place, but due to the limited number of women with these comorbidities, we could not provide reliable answers. Additionally, our study is a retrospective cohort which, due to lack of randomization, may be a source of bias.

CONCLUSIONS

The presented study has shown that concomitant disease during pregnancy may have an impact on some safety and effectiveness outcomes. Pregnant women with a disease compared to healthy ones had higher risk of Caesarean section if were treated by misoprostol, however, this effect was not observed for dinoprostone. On the other side, the presence of a disease caused the time between drug implementation and delivery was longer if dinoprostone was used. Dinoprostone was also more beneficial than misoprostol to get vaginal delivery if these two drugs were compared exclusively in the group of mothers with a disease. Considering child's health, the presence of a disease and mother's age over 35 was associated with lower Apgar scores if preinduction method was by misoprostol.

Although, our results are novel in this area, and require further investigation, we believe, they may help clinicians to make better clinical decisions even at this stage of research.

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Conflict of interest

The authors declare no conflict of interest.

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Factors associated with caesarean section in women referred for preinduction — a nested case-control study in dinoprostone and misoprostol groups

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ABSTRACT

Objectives: Induction of labour is a beneficial perinatal procedure, but may be associated with some risks. The aim of this study was to identify factors associated with the need for Caesarean section in women referred for preinduction with dinoprostone and misoprostol.

Material and methods: It was a retrospective cohort study of 560 pregnant women who underwent labour induction for medical reasons. Analyses were performed separately in the dinoprostone and misoprostol group. Above other characteristics, the diameters of the pelvis and abdominal circumference of pregnant women were analysed.

Results: There were some mothers' characteristics like age, weight, BMI, presence of hypothyroidism or diabetes, which were not associated with Caesarean section deliveries.

Women in the misoprostol group with gestational age less than 38 weeks had an increased risk of Caesarean section (OR 2.189; p = 0.041). The analyses of combined effect of mothers age and parity history showed 6.7 (in dinoprostone group) and over 10 times (in misoprostol group) increased the risk of Caesarean section in nulliparous women over 35 years of age.

Conclusions: The increased risk of Caesarean delivery in the dinoprostone group was combined with the intertrochanteric dimensions such as the mother's height measuring less than 165 cm, nulliparity and hypertension. In the misoprostol group, strong risk factors for Caesarean delivery were mothers aged 35 years or more, gestational age less than 38 weeks and nulliparity and hypertension as in dinoprostone group. The oxytocin infusion had increased the risk of Caesarean section only in the combined dinoprostone and misoprostol group. Further high-quality studies are warranted.

Key words: misoprostol; dinoprostone; caesarean section risk factors

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INTRODUCTION

The general aim of labour induction is to improve the perinatal outcome for both the newborn and mother. A successful induction of labour is achieved when it ends with a vaginal delivery within 24 hours minus maternal complications and delivering a healthy newborn in a good condition (e.g., with a high, ≥ 8 Apgar score). Among a variety of available methods, the pharmacological ones, mostly prostaglandins, are more common, but still being extensively investigated. The research tries to find the safest way to induce the delivery of the baby in the most appropriate time, and to identify the clinical parameters which can be used to predict the labor induction outcome [1]. The most common problem and concern for the obstetricians is the need for Caesarean section (C/S), especially an emergency situation, as a result of failed labor induction. Therefore, pregnant women who are at the greatest risk of C/S delivery should be identified to optimize the strategies of treatment. Although the studies showed a variety of possible factors affecting the labor progress, including mother's age, parity, body mass index [2], the use of epidural anesthesia, a method of labor induction [3], and the status of the cervix

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accessed by Bishop score, there is still an open question of which prostaglandin should be chosen and to whom to get the reduction of C/S risk and to improve perinatal outcomes.

The purpose of this study was to identify factors associated with the need for C/S procedures in daily clinical practice, when dinoprostone gel at a dose of 0.5 mg (Prepidil, Pfizer Polska Sp. z o.o.) or misoprostol vaginal insert at a dose of 0.2 mg (Misodel, Ferring Pharmaceuticals Poland sp. z o.o) were applied for labor induction. Besides the commonly used characteristic checks, the aim was to focus on the mother's anthropometric measurements including diameters of the pelvis as well as some related indexes, including proportions of different pelvic diameters to mother's height or estimated fetal birth weight (EFBW) in relation to pelvic diameters.

MATERIAL AND METHODS

The original research was a retrospective cohort study of 560 pregnant women who underwent labor induction for medical reasons at the Obstetric and Perinatology Department at the University Hospital in Cracow, between January 2015 and April 2019. The research was conducted to evaluate the effectiveness and safety of two delivery induction methods, being dinoprostone gel at a dose of 0.5 mg (Prepidil, Pfizer Polska Sp. z o.o.) or misoprostol vaginal insert at a dose of 0.2 mg (Misodel, Ferring Pharmaceuticals Poland sp. z o.o). The study details have been described elsewhere [4]. In brief, first, all women fulfilling the inclusion criteria were identified in the hospital database. Next, all available data was extracted from the hospital electronic database and available paper charts. The following information was recorded at the time of study enrollment: maternal age and body mass index (BMI), number of pregnancies, gestational age, Bishop's score, the mode of delivery - vaginal birth or C/S, selected comorbidities (hypertension, diabetes, hypothyroidism, Streptococcus agalactiae positive culture), ultrasound EFBW, as well as diameters of the pelvis, and abdominal circumference in some pregnant women. Additionally, other data was collected (the indication for induction of labour, time from drug administration to vaginal delivery or time to any (vaginal or by Caesarean section) delivery and time to the onset of labor, maternal complications such as episiotomy, the rupture of perineum, the placenta abruption or placenta arrest, and anaemia requiring blood transfusion), but the daunting analysis of those are the subject of different articles [4]. Neonatal outcomes, such as birth weight, birth length, gender and 1-minute Apgar score were also accessed.

The primary inclusion criteria were as follows: singleton gestation with cephalic presentation requiring labor induction for medical indications, with the cervical state described as ≤4 in the Bishop's score and with no active labor before administration of the drug. Women were excluded if the EFBW was > 4500 g, had any known contraindication to vaginal delivery, or any contraindication for prostaglandins usage.

As the purpose of the study was to identify risk factors associated with C/S, the nested case-control approach had been implemented. Meaning all the C/S deliveries had been identified in the included cohort (these were considered as cases) and they were compared with vaginal deliveries. Analyses were performed separately in the dinoprostone group and in the misoprostol group.

Statistical analysis

For the purpose of the presented study, as the first step we created two groups based on the delivery preinduction method, meaning the dinoprostone group (D group; 350 patients) or the misoprostol group (M group; 210 patients). We considered if the woman had been primarily referred to the dinoprostone group or the misoprostol group. In these groups, characteristics of pregnant women who had vaginal delivery and underwent C/S were compared. In the secondary analyses, which were intended to identify factors associated with the C/S, three groups were created. The basis for that was the identified presence of the third group of pregnant women who received two considered prostaglandins (meaning the leading doctor had decided to use the second drug sometime after the first one). Only a group of women who received dinoprostone first, and as a next step the misoprostol was found (D+M group; 100 patients). The significance of the difference between groups was determined by the parametric t-test or non-parametric the U-Mann-Whitney test, depending on whether the assumption of normal distribution, verified by the Shapiro-Wilk test, had been fulfilled. To identify factors associated with the C/S risk logistic regression models were calculated. In the first step, the mother's age, anthropometric characteristics including diameters of pelvis, parity history, diagnosis of concomitant disease, pre-ripening cervical characteristic and EFBW were analysed in the univariable analyses. Next, the factors showing significant impact were considered for multivariable analyses to identify those which independently were associated with C/S risk. Analyses were done separately in different treatment groups enabling to show determinants which might be different across treatment type. The pair-wise procedure was applied for missingness. The p-value below 0.05 was considered statistically significant. The IBM SPSS Statistics version 26 was used for calculations.

RESULTS

Characteristics of the study groups at admission are shown in Table 1. There were no significant differences in maternal age, weight or BMI at admission, presence of hy-

Table 1. Clinical characteristics of study participants across route of birth delivery status in the dinoprostone and misoprostol groups

	Dinoprostone			Misoprostol		
	Vaginal delivery [n = 242]	Caesarean Section [n = 108]	p-value	Vaginal delivery [n = 125]	Caesarean Section [n = 85]	p-value
Maternal age (years) Mean, (SD) Median (Q1–Q3)	 30.4 (4.6) 30.0 (27.0–34.0)	 30.8 (4.4) 30.0 (28.0–34.0)	$p^{ett} = 0.382$	 30.5 (3.9)* 31.0 (28.0–33.0)	 31.5 (4.5)* 31.0 (28.0–35.0)	$p^{MW} = 0.054$
Weight at admission (kg) Mean, (SD) Median (Q1–Q3)	[n = 102] 79.7 (13.4)* 78.0 (70.0–88.0)	[n = 94] 80.2 (14.5)* 78.0 (71.5–88.3)	$p^{MW} = 0.933$	[n = 37] 78.8 (12.4)* 77.0 (69.5–84.0)	[n = 76] 82.2 (15.5)* 80.5 (70.0–91.8)	$p^{MW} = 0.250$
Height (cm) Mean, (SD) Median (Q1–Q3)	[n = 207] 167.1 (5.7) 167.0 (164.0–171.0)	[n = 105] 164.5 (6.7) 164.0 (160.0–169.0)	$p^{ett} < 0.001$	[n = 110] 166.8 (5.4) 167.0 (163.8–170.0)	[n = 84] 165.8 (6.1) 165.0 (162.0–170.0)	$p^{ett} = 0.231$
Body mass index at admission (kg/m²) Mean, (SD) Median (Q1–Q3)	[n = 102] 28.4 (4.3) 28.4 (24.9–31.2)	[n = 94] 29.6 (4.9)* 29.0 (25.5–32.1)	$p^{MW} = 0.128$	[n = 36] 28.5 (3.5)* 27.4 (25.7–31.5)	[n = 76] 30.0 (5.3)* 29.4 (26.0–33.1)	$p^{MW} = 0.202$
Hypertension	20 (8.3%)	23 (21.3%)	Df = 1 p = 0.001	12 (9.6%)	18 (21.2%)	Df = 1 p = 0.026
Diabetes	57 (23.6)	23 (21.3%)	Df = 1 p = 0.681	15 (12.0%)	11 (12.9%)	Df = 1 p = 0.999
Diabetes — insulin therapy	37 (15.3%)	18 (16.7%)	Df = 1 p = 0.752	9 (7.2%)	8 (9.4%)	Df = 1 p = 0.612
Hypothyroidism	90 (37.2%)	41 (38.0%)	Df = 1 p = 0.905	46 (36.8%)	35 (41.2%)	Df = 1 p = 0.565
GBS	67 (27.7%)	27 (25.0%)	Df = 1 p = 0.606	23 (18.4%)	16 (18.8%)	Df = 1 p = 0.999
Number of pregnancies [n (%)] 1 2 ≥ 3	 145 (59.9%) 57 (23.6%) 40 (16.5%)	 82 (75.9%) 17 (15.7%) 9 (8.3%)	 Df = 2 p = 0.013	 71 (57.6%) 24 (19.2%) 29 (23.2%)	 54 (63.5%) 19 (22.4%) 12 (14.1%)	 Df = 2 p = 0.265
Parity history (current delivery included) [n (%)] 1 2 ≥ 3	 171 (70.7%) 50 (20.7%) 21 (8.7%)	 96 (88.9%) 8 (7.4%) 4 (3.7%)	 Df = 2 p = 0.001	 85 (68.0%) 28 (22.4%) 12 (9.6%)	 74 (87.1%) 7 (8.2%) 4 (4.7%)	 Df = 2 p = 0.005
Nulliparous [n (%)]	168 (69.4%)	94 (87.0%)	Df = 1 p < 0.001	80 (64.0%)	70 (82.4%)	Df = 1 p = 0.005
Miscarriage history [n (%)] no yes	 196 (81.0%) 46 (19.0%)	 93 (86.1%) 15 (13.9%)	 Df = 1 p = 0.287	 96 (76.8%) 29 (23.2%)	 63 (74.1%) 22 (25.9%)	 Df = 1 p = 0.743
Pre-ripening cervical characteristics [n (%)] Dilatation ≤ 1 cm Effacement ≤ 50% Oxytocin use	 224 (92.6%) 230 (95.0%) 98 (40.5%)	 105 (97.2%) 105 (97.2%) 54 (50.0%)	 Df = 1 p = 0.141 Df = 1 p = 0.410 Df = 1 p = 0.103	 109 (87.2%) 112 (89.6%) 11 (8.8%)	 85 (100.0%) 85 (100.0%) 10 (11.8%)	 Df = 1 p = 0.001 Df = 1 p = 0.002 Df = 1 p = 0.640
Gestational age (weeks)# Mean, (SD) Median (Q1–Q3)	 39.8 (1.3)* 40.0 (39.0–41.0)	 39.8 (1.3)* 40.0 (39.0–41.0)	 $p^{MW} = 0.674$	 39.3 (1.7)* 40.0 (39.0–40.0)	 38.7 (2.2)* 39.0 (37.0–40.0)	 $p^{MW} = 0.025$
Estimated birth weight (g) Mean, (SD) Median (Q1–Q3)	[n = 65] 3497.2 (440.1)* 3600.5 (3265.0–3832.0)	[n = 43] 3608.1 (493.7)* 3700.0 (3300.0–3975.0)	$p^{MW} = 0.099$	[n = 65] 3393.4 (530.7)* 3485.0 (3116.5–3748.5)	[n = 48] 3187.5 (627.0) 3225.0 (2850.5–3746.8)	$p^{MW} = 0.086$

*–p < 0.05 by the Shapiro-Wilk test for normal distribution; ett — the t-test for equal variances; MW — the U-Mann-Whitney test, for categorical data p-value calculated by the chi-2 test; Df — degrees of freedom; # — at time of administration of the first dose of the drug

Table 2. Mother's anthropometric characteristics of the pelvis across route of birth delivery status in the dinoprostone and misoprostol groups

	Dinoprostone			Misoprostol		
	Vaginal delivery [n = 242]	Caesarean Section [n = 108]	p-value	Vaginal delivery [n = 125]	Caesarean Section [n = 85]	p-value
Diameters of the pelvis						
External conjugate (cm) Mean, (SD) Median (Q1–Q3)	[n = 152] 21.1 (1.6)* 21.0 (20.0–22.0)	[n = 75] 21.0 (1.7)* 21.0 (20.0–22.0)	$p^{MW} = 0.981$	[n = 109] 21.1 (1.7)* 21.0 (20.0–22.0)	[n = 74] 21.3 (1.6)* 21.0 (20.0–22.0)	$p^{MW} = 0.757$
Interspinal dimension (cm) Mean, (SD) Median (Q1–Q3)	[n = 154] 24.0 (1.7)* 24.0 (23.0–25.0)	[n = 75] 23.8 (1.4)* 24.0 (23.0–25.0)	$p^{MW} = 0.489$	[n = 109] 24.0 (1.4)* 24.0 (23.0–25.0)	[n = 74] 23.7 (1.5)* 24.0 (23.0–25.0)	$p^{MW} = 0.260$
Intercristal dimension (cm) Mean, (SD) Median (Q1–Q3)	[n = 154] 27.8 (1.9)* 28.0 (26.0–29.0)	[n = 75] 27.6 (1.6)* 28.0 (26.0–29.0)	$p^{MW} = 0.502$	[n = 109] 27.7 (1.6)* 28.0 (26.5–29.0)	[n = 74] 27.7 (2.1)* 27.0 (26.8–29.0)	$p^{MW} = 0.838$
Intertrochanteric dimension (cm) Mean, (SD) Median (Q1–Q3)	[n = 154] 33.3 (2.7)* 33.0 (32.0–35.0)	[n = 75] 32.3 (2.3)* 32.0 (31.0–34.0)	$p^{MW} = 0.002$	[n = 109] 32.6 (2.2)* 33.0 (31.0–34.0)	[n = 74] 33.0 (2.2)* 33.0 (31.0–34.0)	$p^{MW} = 0.408$

pothyroidism, diabetes or GBS between vaginal and C/S deliveries independently whether the D or M groups were investigated (Tab. I). A statistically significant difference was found in a mother's height, as women who delivered by the vaginal route were taller than the C/S group. The difference, however, was observed in the D group ($p < 0.01$) only. In both (D and M) groups, women in the C/S delivery groups were more frequently diagnosed with hypertension, or they were nulliparous. What was interesting were the differences in pre-ripening cervical characteristics and gestational age being noticed in the M group only (Tab. 1).

We have compared pelvis diameters, maternal abdominal circumference and some created indexes which included diameters of the pelvis in relation to mother's height, abdominal circumference to height, and additionally EFBW in relation to mother's height and EFBW to available pelvis diameters. The measurements which were found to be significantly different between vaginal delivery and C/S groups were the intertrochanteric dimensions, which were lower in the C/S deliveries observed in the D group, and the EFBW to height index which were higher in the C/S deliveries, also in the D group (Tab. 2 and 3).

Analysis of neonatal outcomes across the route of birth delivery status in the D and M groups show significant differences in Apgar scores. In both prostaglandin groups neonates delivered by C/S had on average, less points in Apgar scale (means: 9.5 *vs.* 9.8 points, and 9.1 *vs.* 9.8 points), while only the M group had lower birth weight (3229g in C/S *vs.* 3405 g in vaginal delivery group; $p = 0.038$) (Tab. 4). It is worth noting the gestational age was also significantly younger in the C/S as compared to the vaginal delivery group observed in the M group (38.7 *vs.* 39.3; $p = 0.025$), but not in the D group (Tab. 1).

The next step was the analysis of possible factors associated to the C/S risk in the three (D, M and D + M) preinduction groups. Among pregnant women, who were treated by dinoprostone, height (both, considered as categorical < 165 cm *vs.* ≥ 165 cm: OR: 2.1, or as continuous: for each 1 cm increase: OR: 0.9), and intertrochanteric dimension (continuous, for each 1 cm increase OR: 0.8), and additionally the number of pregnancies, nulliparity, and hypertension were significantly associated with C/S risk. In the M group, higher risk has been observed in mothers which were over 35 years of age (OR 2.5) and in their gestational age less than 38 weeks (OR 2.0). Nulliparity and hypertension were also risk factors identified in this group (Tab. 5). In the D + M group statistically significant clinical features were hypertension and treatment by oxytocin. After univariable analyses, the variables, which were identified as associated significantly with C/S risk, were put in the multivariable model to check whether some of them are independent risk factors for C/S delivery. Across different preinduction groups hypertension was identified as an independent risk factor for each treatment strategy. Additionally, nulliparity was associated with C/S delivery in both, the D group and the M group. Gestational age less than 38 weeks was a risk factor for women treated by misoprostol, and oxytocin use for those who received both preinduction drugs. Mothers over 35 years of age seemed to be a risk factor if the misoprostol was used, whereas height (being taller) decreased the risk if the dinoprostone was used.

Finally, we tried to look at the combined effect of parity history and the mother's age. The study showed 6.7 and more than 10 times the increased risk of Caesarean section in nulliparous women aged over 35 years in both D and M groups, respectively (Fig. 1).

Table 3. Mothers' anthropometric indexes across route of birth delivery status in the dinoprostone and misoprostol groups

	Dinoprostone			Misoprostol		
	Vaginal delivery [n = 242]	Caesarean Section [n = 108]	p-value	Vaginal delivery [n = 125]	Caesarean Section [n = 85]	p-value
External conjugate/height [%] Mean, (SD) Median (Q1–Q3)	[n = 134] 12.6 (0.9)* 12.5 (12.0–13.0)	[n = 72] 12.8 (1.0)* 12.7 (12.2–13.2)	$p^{MW} = 0.322$	[n = 96] 12.7 (1.2)* 12.7 (12.0–13.1)	[n = 73] 12.8 (0.9)* 12.6 (12.2–13.3)	$p^{MW} = 0.323$
Interspinal dimension/height [%] Mean, (SD) Median (Q1–Q3)	[n = 135] 14.4 (1.03)* 14.4 (13.6–15.1)	[n = 72] 14.5 (1.11) 14.5 (13.6–15.2)	$p^{MW} = 0.795$	[n = 96] 14.4 (0.84) 14.4 (13.8–14.9)	[n = 73] 14.3 (0.94) 14.3 (13.7–15.0)	$p^{tt} = 0.744$
Intercristal dimension/height [%] Mean, (SD) Median (Q1–Q3)	[n = 135] 16.7 (1.01) 16.7 (15.9–17.2)	[n = 72] 16.7 (1.11) 16.7 (16.1–17.5)	$p^{tt} = 0.682$	[n = 96] 16.5 (0.95) 16.7 (15.9–17.1	[n = 73] 16.7 (1.23)* 16.7 (16.0–17.3)	$p^{MW} = 0.479$
Intertrochanteric dimension/height [%] Mean, (SD) Median (Q1-Q3)	[n = 135] 20.0 (1.50)* 19.9 (18.9–20.8)	[n = 72] 19.6 (1.50) 19.4 (18.4–20.6)	$p^{MW} = 0.080$	[n = 96] 19.5 (1.43) 19.4 (18.6–20.6)	[n = 73] 19.9 (1.42) 20.0 (18.8–20.8)	$p^{tt} = 0.066$
Abdominal circumference (cm) Mean, (SD) Median (Q1–Q3)	[n = 143] 109.4 (8.9) 108.0 (103.0–114.0)	[n = 72] 109.7 (8.4) 109.5 (103.3–116.0)	$p^{tt} = 0.828$	[n = 104] 108.2 (8.0)* 107.0 (103.0–112.0)	[n = 71] 109.6 (9.6) 108.0 (103.0–115.0)	$p^{MW} = 0.226$
Abdominal circumference/height [%] Mean, (SD) Median (Q1–Q3)	[n = 127] 65.2 (5.1)* 64.7 (61.2–68.3)	[n = 69] 66.5 (5.6) 66.3 (62.4–69.7)	$p^{MW} = 0.124$	[n = 91] 64.8 (4.9)* 64.6 (60.9–68.5)	[n = 70] 66.3 (5.8) 66.0 (62.2–69.7)	$p^{MW} = 0.063$
EFBW/height [g/cm]	[n = 57] 21.0 (2.5)* 21.4 (19.3–22.9)	[n = 42] 21.8 (3.2) 22.0 (19.9–23.9)	$p^{MW} = 0.049$	[n = 58] 20.6 (2.9)* 21.2 (18.8–22.5)	[n = 48] 19.3 (3.9) 19.5 (17.1–22.3)	$p^{MW} = 0.083$
EFBW/abdominal circumference	[n = 46] 32.2 (3.9)* 32.5 (29.9–35.3)	[n = 31] 32.3 (5.0) 33.8 (28.2–36.2)	$p^{MW} = 0.729$	[n = 53] 31.7 (4.4)* 32.2 (29.3–34.4)	[n = 40] 30.2 (5.3) 30.5 (26.3–35.1)	$p^{MW} = 0.159$
EFBW/External conjugate	[n = 47] 264.9 (22.3) 166.1 (151.0–180.8)	[n = 33] 170.0 (27.1) 176.2 (155.0–184.4)	$p^{tt} = 0.362$	[n = 58] 161.3 (23.5)* 165.5 (145.5–178.9)	[n = 43] 155.0 (32.7) 160.0 (132.7–180.6)	$p^{MW} = 0.371$
EFBW/Interspinal dimension	[n = 48] 146.4 (17.8)* 150.0 (135.2–157.0)	[n = 33] 149.2 (24.2) 152.2 (132.7–168.1)	$p^{MW} = 0.328$	[n = 58] 141.1 (21.8)* 147.5 (130.5–154.4)	[n = 43] 138.3 (27.9) 142.9 (120.0–156.5)	$p^{MW} = 0.486$
EFBW/Intercristal dimension	[n = 48] 125.2 (15.9)* 131.1 (115.4–136.3)	[n = 33] 128.9 (19.9) 132.1 (117.4–143.7)	$p^{MW} = 0.291$	[n = 58] 122.1 (18.2)* 127.2 (110.3–135.6)	[n = 43] 117.9 (22.5) 120.0 (104.3–131.9)	$p^{MW} = 0.239$
EFBW/Intertrochanteric dimension	[n = 48] 104.5 (13.5) 105.7 (97.4–114.8)	[n = 33] 110.2 (17.6) 111.8 (101.6–124.6)	$p^{tt} = 0.104$	[n = 58] 104.5 (15.8)* 106.5 (93.2–118.4)	[n = 43] 99.0 (18.8)* 103.3 (85.9–111.8)	$p^{MW} = 0.178$

DISCUSSION

Labor induction is a perinatal intervention which is becoming more common worldwide and is of growing importance providing the opportunity to treat unfavorable cervixes. Although prostaglandin medications have been used for several years [5], there is still a need to get more knowledge about maternal and fetal characteristics which are associated with an increased risk of C/S. This issue was addressed by our study, through the investigation of the two prostaglandins, which are most often used in clinical practice, dinoprostone and misoprostol.

There are several clinical and anthropometric features which may cause the necessity of C/S delivery. First, a well-known determinant is nulliparity and cervical ripeness status at the beginning of the procedure. Although the preinduction with prostaglandins was introduced into clinical practice, the risk of vaginal labor failure is bigger when dealing with an unripe cervix, especially in nulliparous patients [6–7]. Similar effects have been observed in our study. Additionally, our study revealed nulliparity as an independent risk factor of C/S regardless of the type of preinduction method used. Maslow and Sweeny showed also an almost three-fold increased risk of C/S among nulliparas and a two-fold increase among parous women who underwent induction compared with nulliparas and multiparous women who did not [8]. Although the last study

Table 4. Neonatal outcomes across route of birth delivery status in the dinoprostone and misoprostol groups

	Dinoprostone			Misoprostol		
	Vaginal delivery [n = 242]	Caesarean Section [n = 108]	p-value	Vaginal delivery [n = 125]	Caesarean Section [n = 85]	p-value
Apgar score (points) Mean, (SD) Median (Q1–Q3)	9.8 (0.7)* 10 (10–10)	9.5 (1.3)* 10 (9–10)	$p^{MW} < 0.001$	9.8 (1.0)* 10 (10–10)	9.1 (1.7)* 10 (9–10)	$p^{MW} < 0.001$
Apgar score ≤ 6 points at the 1st min (n, %)	3 (1.2%)	5 (4.6%)		3 (2.4%)	9 (10.6%)	
Apgar score 7–8 points at the 1st min (n, %)	8 (3.3%)	6 (5.6%)		4 (3.2%)	9 (10.6%)	
Apgar score 9-10 points at the 1st min (n, %)	231 (95.5%)	97 (89.8%)	$p^{F} = 0.081$	118 (94.4%)	67 (78.8%)	$p^{F} = 0.003$
Birth weight (g) Mean, (SD) Median (Q1–Q3)	3507 (426)* 3545 (3242–3800)	[n = 107] 3573 (479)* 3580 (3230–3880)	$p^{MW} = 0.216$	3405 (487)* 3460 (3080–3735)	3229 (620) 3240 (2805–3695)	$p^{MW} = 0.038$
Birth length (cm) Mean, (SD) Median (Q1–Q3)	55.6 (2.8)* 56.0 (54.0–57.0)	[n=107] 55.5 (3.1) 56.0 (53.0–58.0)	$p^{MW} = 0.946$	54.9 (3.2)* 55.0 (53.0–57.0)	54.2 (3.5) 54.0 (52.0–56.0)	$p^{MW} = 0.103$
			Df = 1			Df = 1
Female (n, %)	125 (51.7%)	44 (40.7%)	$p^{chi2} = 0.065$	63 (50.4%)	46 (54.1%)	$p^{chi2} = 0.673$

* – $p < 0.05$ by the Shapiro-Wilk test for normal distribution; MW — the U Mann-Whitney test; chi2 — the chi-squared test with 1degree of freedom; F — the exact Fisher's test

is not unequivocally comparable with the present one, it shows a trend of higher risk depending on parity. Like in the other study with dinoprostone agents, although on a smaller study group where multiple logistic regression analysis also showed that the gravidity (OR = 0.61, 95% CI 0.408–0.892; p = 0.011) was an independent predictor of successful labor induction, with no statistically significant differences in maternal age, gestational age, body mass index, fetal sex or the Bishop score at the time of admission [9].

Among other parameters of possible importance in predicting likelihood of successful labor induction, Pevzner et al., was pointing out the maternal body mass index (BMI) less than 30 and height greater than 165 cm [10]. The analyses of those parameters in our database revealed some similarities, especially when considering parity and mother's height. In the dinoprostone group, the height of women who gave vaginal birth was 167 cm average compared to 164 cm in those who underwent C/S. Patients in the M and D groups, however, had no differences in body mass index and maternal weight at admission. Our study provided an opportunity to analyse pelvic dimensions and abdominal circumference of pregnant women. These features were of our special interest because they are seldom listed as an important parameter influencing labor induction outcome. We have checked whether pelvimetric measurements in conjunction with EFBW or with mother's height have any correlation with the mode of delivery. The majority of our results, however, were not statistically significant (Tab. 5). Only intratrochanteric diameter in the D group showed a difference, as a bigger dimension was observed in the vaginal delivery subgroup. It was associated, with high probability and maternal height, which was also statistically greater in that subgroup. When put together the obstetric pelvimetry with EFBW the risk of cephalopelvic disproportion should be reduced [11–12], which is also a basic rule of proper qualification of pregnant woman to labour induction procedures and these relationships have been confirmed by our study as well.

Pevzner showed that fetal weight over 4000 g may be a risk factor of induction failure [10]. Other research showed important differences in average birth weight of 3421.11 ± 368.14 in successful *vs.* 3566.36 ± 345.16 in the failed induction group (p = 0.033) [9]. Our study showed important differences in birth weight in the M group, but in an opposite way, as it turns out that smaller babies were born by C/S (3229 ± 620 vs 3405 ± 487; pMW = 0.038). Although the EFBW is routinely performed during the ultrasound testing at the admission to the hospital, it is not obligatory to introduce it into the electronic database in our hospital and therefore some of records were missing in the current analysis, making the groups smaller sizes. This may be a reason for not reaching the statistical significance of ultrasonographic fetal weight estimation, especially in the misoprostol group (Tab. 1). When we looked closer we saw that in the M group, the birth weight in the C/S subgroup might be an effect of gestational age, while as a possible C/S risk factor (OR 2.189; p = 0.041) the

Table 5. Analysis of possible factors associated with Caesarean section in the dinoprostone, and misoprostol, and dinoprostone with misoprostol groups

	Dinoprostone [n = 250]				Misoprostol [n = 210]				Dinoprostone+misoprostol [n = 100]			
	OR	95% CI		p-value	OR	95% CI		p-value	OR	95% CI		p-value
Mother's age (years)	1.008	0.951	1.069	0.778	1.067	0.997	1.142	0.062	1.082	0.968	1.208	0.164
Mother's age > 35 years	1.128	0.581	2.189	0.721	2.510	1.301	4.845	0.006	3.117	0.847	11.467	0.087
Weight at admission (kg)	0.994	0.971	1.019	0.657	1.018	0.989	1.048	0.215	1.019	0.976	1.063	0.393
Weight at admission > 78 kg$	0.977	0.499	1.912	0.946	1.267	0.578	2.778	0.555	0.920	0.304	2.790	0.884
Height (cm)	0.930	0.885	0.977	0.004	0.969	0.922	1.020	0.226	0.940	0.874	1.011	0.094
Height < 165cm	2.125	1.182	3.820	0.012	1.308	0.729	2.347	0.368	1.778	0.762	4.147	0.183
Body mass index at admission (kg/m^2)	1.032	0.958	1.112	0.405	1.075	0.980	1.178	0.125	1.100	0.965	1.253	0.153
BMI > 30 kg/m^2	0.958	0.477	1.923	0.904	1.996	0.863	4.616	0.106	1.687	0.551	5.171	0.360
Abdominal circumference [cm]	0.990	0.945	1.036	0.657	1.019	0.984	1.055	0.290	1.005	0.958	1.055	0.834
External conjugate (cm)	0.939	0.710	1.241	0.658	1.050	0.882	1.249	0.584	0.976	0.783	1.216	0.826
Interspinaldimention (cm)	0.878	0.695	1.109	0.276	.892	0.727	1.094	0.272	0.974	0.749	1.266	0.844
Intercristal dimension (cm)	0.876	0.707	1.086	0.228	1.020	0.868	1.200	0.807	1.016	0.805	1.282	0.897
Intertrochanteric dimension (cm)	0.796	0.670	0.944	0.009	1.014	0.922	1.114	0.775	0.850	0.696	1.038	0.111
External conjugate/height [%]	1.247	0.767	2.030	0.373	1.152	0.858	1.547	0.346	0.985	0.661	1.467	0.940
Interspinal dimension/height [%]	1.087	0.749	1.576	0.661	0.944	0.668	1.334	0.744	1.107	0.739	1.660	0.622
Intercristal dimension/height [%]	1.043	0.713	1.525	0.830	1.189	0.892	1.583	0.237	1.063	0.711	1.587	0.767
Intertrochanteric dimension/height [%]	0.790	0.599	1.041	0.094	1.241	0.995	1.548	0.055	0.836	0.603	1.160	0.283
abdominal circumference/height [%]	1.037	0.960	1.119	0.360	1.057	0.995	1.122	0.071	1.034	0.951	1.123	0.435
EFBW/height [g/cm]	1.227	0.988	1.524	0.065	0.895	0.797	1.005	0.062	1.031	0.818	1.298	0.797
EFBW/abdominal circumference	1.047	0.892	1.228	0.575	0.940	0.861	1.025	0.163	0.994	0.850	1.162	0.939
EFBW/External conjugate	1.018	0.988	1.049	0.233	0.992	0.978	1.006	0.272	1.006	0.980	1.034	0.647
EFBW/Interspinal dimension	1.016	0.984	1.048	0.333	0.995	0.979	1.011	0.555	1.000	0.967	1.033	0.988
EFBW/Intercristal dimension	1.028	0.986	1.072	0.190	0.990	0.971	1.010	0.328	1.002	0.967	1.039	0.895
EFBW/Intertrochanteric dimension	1.038	0.991	1.087	0.112	0.981	0.959	1.005	0.116	1.020	0.976	1.066	0.379
Number of pregnancies			For trend	0.014			For trend	0.220			For trend	0.255
1	1 (ref)				1 (ref)				1 (ref)			
2	0.458	0.219	0.959	0.038	1.041	0.518	2.092	0.910	0.958	0.310	2.958	0.941
≥ 3	0.412	0.171	0.994	0.049	0.589	0.280	1.240	0.164	0.240	0.028	2.087	0.196
Parity history (current delivery included)			For trend	0.005			For trend	0.013			For trend	0.135
1	1 (ref)				1 (ref)				1 (ref)			
2	0.284	0.114	0.705	0.007	0.284	0.117	0.688	0.005	0.402	0.079	2.043	0.272
≥ 3	0.321	0.091	1.129	0.077	0.473	0.159	1.405	0.178	—	—	—	#
Nulliparous	3.146	1.506	6.573	0.002	2.492	1.295	4.797	0.006	2.353	0.605	9.158	0.217
Miscarriage history	0.751	0.348	1.617	0.464	1.126	0.595	2.132	0.715	0.600	0.194	1.861	0.377
Pre-ripening cervical characteristics												
Dilatation ≤ 1 cm	3.622	0.817	16.048	0.090	—	—	—	#	—	—	—	#
Effacement ≤ 50%	2.123	0.458	9.835	0.336	—	—	—	#	0.633	0.038	10.430	0.749
Oxytocin use	1.117	0.638	1.956	0.698	1.352	0.547	3.339	0.514	2.947	1.282	6.774	0.011
Gestational age (weeks)	0.899	0.702	1.150	0.396	0.841	0.727	0.973	0.020	1.109	0.846	1.455	0.453
Gestational ageless than 38 weeks	2.781	0.676	11.449	0.157	2.024	1.009	4.060	0.047	0.764	0.180	3.251	0.715
Estimated birth weight (for change by 100g)	1.112	0.982	1.260	0.095	0.941	0.880	1.005	0.072	0.999	0.874	1.143	0.992
Hypertension	2.690	1.233	5.869	0.013	2.647	1.209	5.794	0.015	3.677	1.025	13.193	0.046
Diabetes	0.699	0.350	1.394	0.309	1.274	0.558	2.909	0.565	1.225	0.461	3.252	0.684
Diabetes — insulin therapy	0.910	0.417	1.984	0.812	1.487	0.536	4.129	0.446	1.491	0.521	4.266	0.456
Hypothyroidism	1.153	0.645	2.062	0.631	1.221	0.696	2.142	0.487	0.690	0.304	1.562	0.373
GBS	0.790	0.414	1.509	0.476	1.082	0.539	2.174	0.825	0.970	0.387	2.428	0.948

OR — odds ratio; CI — confidence interval; EFBW — estimated fetal birth weight; # — cannot estimate model parameters due to limited sample size; $ — the observed median in the vaginal delivery route group (total)

Table 6. Identified risk factors of Caesarean section across different preinduction groups — multivariable analysis

	Dinoprostone [n = 250]				Misoprostol [n = 210]				Dinoprostone + Misoprostol [n = 100]			
	OR	95% CI		p-value	OR	95% CI		p-value	OR	95% CI		p-value
Mother's age > 35 years	#				3.252	1.561	6.778	0.002	#			
Height (cm)	0.929	0.882	0.979	0.006	#				#			
Nulliparous	3.669	1.665	8.085	0.001	3.341	1.608	6.940	0.001	#			
Gestational age less than 38 weeks	#				2.189	1.032	4.642	0.041	#			
Hypertension	3.586	1.434	8.967	0.006	2.278	0.995	5.211	0.051	4.146	1.096	15.684	0.036
Oxytocin use	#				#				3.149	1.333	7.441	0.009

OR — odds ratio; CI — confidence interval; # — not considered for the model as a significant effect in the univariable analysis was not observed; additionally intertrochanteric dimension was removed from the dinoprostone analysis due to too high number of missingness leading to no stable model estimates

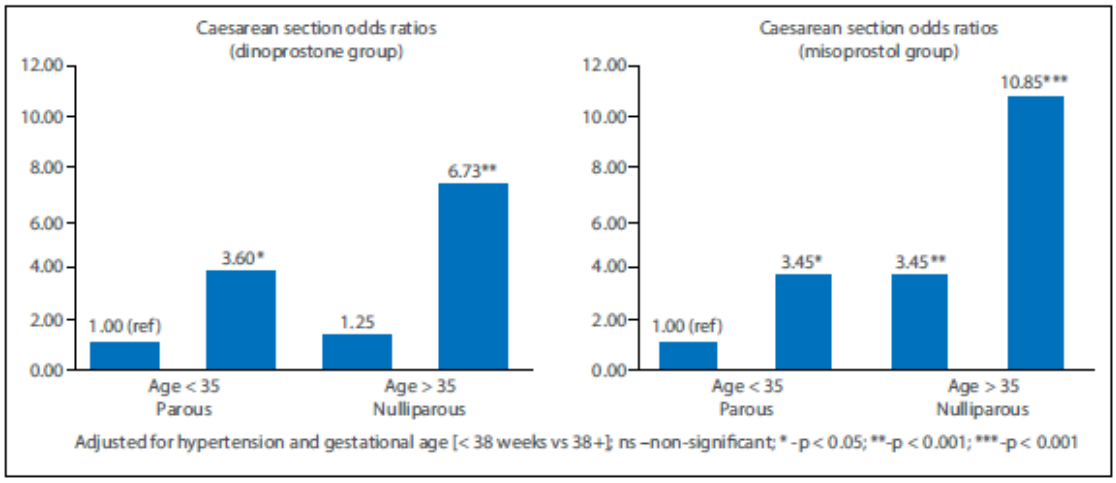

Figure 1. Combined effect of mother's age and parity history on the Caesarean section risk estimates

gestational age less than 38 weeks was found, which was not observed in dinoprostone group. Studies analysing preterm deliveries showed that vaginal live birth rates increased with gestational age [13], and, additionally, lower gestational age at delivery was a significant predictor of ripening failure [14].

In general, the aim of this study was to compare the two most used prostaglandins separately and if something happened, the two-drug group (group M + D). We also checked if oxytocin augmentation has any influence on the final results. What is interesting is that we have found that only in combination of D and M the oxytocin infusion had increased the risk of C/S. Misoprostol alone probably has not only cervical ripening capability, but also labor induction properties [15] and is more cost-effective than dinoprostone [16]. But there is still a group of patients irresponsive to any labour agents, which needs further studies.

No significant differences in maternal age and miscarriage history were found among the M and D groups, which stays in compliance with other studies [7, 10]. Multivariable analysis, however, showed that mothers aged over 35 years in the misoprostol group increased the risk of C/S 3.2 times with statistical significance ($p = 0.002$). The current results support the findings of previous studies on advanced maternal age [17–19]. Only ages > 35 years, and not the age itself, was a statistically significant predictor of caesarean delivery rate in the misoprostol group. When further analyzes were performed on the combined effects of mother's age and parity history on the caesarean section risk, adjusted for hypertension and gestational age, it revealed that nulliparous women over 35 years of age in the D and M groups had 6.73- and 10.85-times higher risk, respectively, for C/S than parous pregnant women below 35 years of age (Fig. 1). Another study showed that primigravidas induced with misoprostol had a higher C/S rate compared to multiparas (40.58% vs. 16.13%), and what is more, there were statistically important differences in average age of those women, as primigravidas and multiparas

were 27.71 ± 5.45 and 31.58 ± 5.68 years old, respectively (p = 0.0016) [20].

Other study also showed that maternal age over 35 years and nulliparity were significantly associated with caesarean delivery when induced with dinoprostone gel [2]. On the other hand, our study did not identify gestational diabetes mellitus as associated with the route of delivery, likewise it was published by Hawkins et al., study with misoprostol induction [21]. These results, however, differ from other observations [2], and in contrary to hypertension which came out in our work, to be very strong predictor of C/S and which stays in compliance with Sievert et al. [2, 22].

The presented study, however, has some limitations. First, was a surprising number of patients do not have available data on pelvic diameters, which decreased the power of our conclusions in this area, which requires further investigation. Next, our study was performed in a nested case-control design. The primary investigation, therefore, did not focus on risk groups, as one of underlying inclusion criteria. As a next step, it would be useful to perform some observations in well-defined risk groups, to check the prospective observation the C/S risk estimates across different preinduction methods. We would like to mention also that there are many more factors possibly contributing to C/S risk. The most important, however, as mother's age, parity history, increased BMI, extremes of neonatal birth weight or complicated pregnancy and others were controlled in our study by the inclusion criteria or by implementation of multivariable statistical analyses.

In summary, the main findings of the present study were that the increased risk of Caesarean delivery in dinoprostone group was combined with the mother's height less than 165 cm, nulliparity and hypertension. Subsequently in the misoprostol group, strong risk factors of Caesarean delivery were mother's aged 35 or more, gestational age less than 38 weeks and nulliparity and hypertension as in dinoprostone group. Although, in both M and D groups, nulliparous women aged 35 or more years had significantly bigger risk of Caesarean section than multiparous women. The risk was slightly bigger in misoprostol group. Therefore, in our opinion, the aforementioned features should be considered before the decision about the preinduction method. Further high-quality studies assessing the possible Caesarean section risk factors of misoprostol and dinoprostone in selected groups of patients are warranted.

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Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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OŚWIADCZENIA WSPÓŁAUTORÓW

Kraków, dnia 1.12.2021

Prof. dr hab. n. med. Hubert Huras

OŚWIADCZENIE

Jako współautor prac pt.: "Gornisiewicz T, Kusmierska-Urban K, Huras H, Galas A. Comparison of Misoprostol versus Dinoprostone for delivery induction among pregnant women without concomitant disease. Ginekol Pol. 2020;91(12):726-732. doi: 10.5603/GP.2020.0119." ; "Gornisiewicz T, Huras H, Kusmierska-Urban K, Galas A. Pregnancy-related comorbidities and labor induction — the effectiveness and safety of dinoprostone compared to misoprostol. Ginekol Pol 2021;92(9):647-658. DOI: 10.5603/GP.a2021.0092 Pubmed: 34105752" ; "Gornisiewicz, Kusmierska-Urban K, Huras H, Galas A. Factors associated with caesarean section in women referred for preinduction — a nested case-control study in dinoprostone and misoprostol groups. DOI:10.5603/GP.a2021.0168 Online ahead of print."

Oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie prac w formie publikacji to:

pomoc w zaprojektowaniu badania, krytyczna rewizja powstałych manuskryptów.

Jednocześnie wyrażam zgodę na przedłożenie w/w prac przez lek. Teresę Górnisiewicz jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, że samodzielna i możliwa do wyodrębnienia część ww. prac wskazuje indywidualny wkład lek. Teresy Górnisiewicz przy opracowywaniu koncepcji, zebraniu materiału, opracowaniu i interpretacji wyników tych prac.

Klinika Położnictwa i Perinatologii UJ CM

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Kraków, dnia 04 listopad 2021

Dr hab. n. med. Aleksander Gałaś

OŚWIADCZENIE

Jako współautor prac pt.: "Gornisiewicz T, Kusmierska-Urban K, Huras H, Galas A. Comparison of Misoprostol versus Dinoprostone for delivery induction among pregnant women without concomitant disease. Ginekol Pol. 2020;91(12):726-732. doi: 10.5603/GP.2020.0119." ; "Gornisiewicz T, Huras H, Kusmierska-Urban K, Galas A. Pregnancy-related comorbidities and labor induction — the effectiveness and safety of dinoprostone compared to misoprostol. Ginekol Pol 2021;92(9):647-658. DOI: 10.5603/GP.a2021.0092 Pubmed: 34105752" ; "Gornisiewicz, Kusmierska-Urban K, Huras H, Galas A. Factors associated with caesarean section in women referred for preinduction — a nested case-control study in dinoprostone and misoprostol groups. DOI:10.5603/GP.a2021.0168 Online ahead of print."

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pomoc interpretacji wyników i analiza statystyczna.

Jednocześnie wyrażam zgodę na przedłożenie w/w prac przez lek. Teresę Górnisiewicz jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

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Dr n. med. Katarzyna Kuśmierska-Urban

OŚWIADCZENIE

Jako współautor prac pt.: "Gornisiewicz T, Kusmierska-Urban K, Huras H, Galas A. Comparison of Misoprostol versus Dinoprostone for delivery induction among pregnant women without concomitant disease. Ginekol Pol. 2020;91(12):726-732. doi: 10.5603/GP.2020.0119." ; "Gornisiewicz T, Huras H, Kusmierska-Urban K, Galas A. Pregnancy-related comorbidities and labor induction — the effectiveness and safety of dinoprostone compared to misoprostol. Ginekol Pol 2021;92(9):647-658. DOI: 10.5603/GP.a2021.0092 Pubmed: 34105752" ; "Gornisiewicz, Kusmierska-Urban K, Huras H, Galas A. Factors associated with caesarean section in women referred for preinduction — a nested case-control study in dinoprostone and misoprostol groups. DOI:10.5603/GP.a2021.0168 Online ahead of print."

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Kuśmierska-Urban Katarzyna