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# In Vitro Susceptibility Of Tigecycline Among *Acinetobacter Baumanii* Clinical Isolates From a Hospital in Indonesia

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**Abstract**

*Acinetobacter baumanii* (*A. baumanii*) has arisen as the most important cause of nosocomial infection, typically in severely ill patients with many comorbidities and medical supportive devices. Tigecycline is a therapeutic option for treating this infection because of its potential ability against wide spectrum of bacterias, including multi-drug resistance *A. baumannii* (MDRAB). Our study determine the in vitro susceptibility of tigecycline against *A. baumanii* isolates and the emergence of MDRAB. The frequency of isolates that were not inhibited at MIC ≤ 0.5 µg/ml was 50.46%, at MIC = 1µg/ml was 2.38%, and at MIC = 2 µg/ml was 19.07%. The susceptibility rate of tigecycline against *A. baumanii* was 68.27% in 2015, 79.58% in 2016, and 67.87% in 2017. In vitro result demonstrated that tigecycline had good value of MIC against *A. baumanii* at the range of 0.5 to 2 µg/ml.

***Keywords:*** **multi-drug resistance *A. baumannii* (MDRAB), tigecycline, susceptibility**

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## Introduction

*A. baumanii* is a pleomorphic Gram negative bacilli, that accounts for approximately 17.44% of reported nosocomial infections in Indonesia.[1] This organism typically affects immunocompromised patients with medical devices, with high incidences and difficult-to-treat infection due to the resistance of the bacteria. In the past decades, the rise of severe infection by this bacteria was related to the lower proportion of susceptible *A. baumanii* isolates which induced high mortality.[2,3]

Over the past few decades, clinicians have noticed a significant increase in the rate of multi-drug resistance *A. baumannii* (MDRAB). The emergence of this multi-drug resistant organism has impacted on the choice of antibiotic therapy which becoming limited, and subsequently to prolonged length-of-stay along with inflated general costs of hospitalization.
The new molecule tigecycline is one of the few therapeutic options against MDRAB.[2-5]

Tigecycline, a newer derivate minocycline, is a glycylcyclines that strongly counter a broad range of both Gram negative and positive bacterial activity, including *Acinetobacter spp* and multiple isolates.[4,6] The addition of a 9-t-butyl-glycylamido side chain affects the bacterial ribosomes with high affinity and active drug efflux, therefore inhibits the primary resistance mechanisms of tetracycline.[4,6-7]

Information regarding this organism and their antibiotic susceptibility profiles among hospitalized patients in Indonesia is scarce. In our hospital, the multi-drug resistant organisms was prevalent across both Gram positive and negative bacterial genera due to excessive antibiotic use. Thus, the objective of the present study was to appraise in vitro susceptibility of tigecycline against *A. baumanii* isolates and the emergence of MDRAB.

## Materials and Methods

This study involved 692 clinical isolates of *A. baumanii* from patients in a hospital located in Tangerang, Indonesia from January 2015 to December 2017. This was a retrospective descriptive study on microbiology laboratory data with one isolate for each patient. *Acinetobacter baumanii* identification and antibiotic susceptibility testing was evaluated by colony morphological features, Gram-staining and the VITEX-2 Compact® (Biomérieux, France) system.

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All isolates were testing for susceptibility to β-lactams (ampicillin/sulbactam, piperacillin/tazobactam, cefazolin,ceftazidime, ceftriaxone, and meropenem); aminoglycosides (amikacin, gentamicin); fluoroquinolones (ciprofloxacin,levofloxacin);trimethoprim/sulfa methoxazole; and tigecycline.

The recommendation for MIC and susceptibility breakpoint based on Clinical and Laboratory Standard Institute (CLSI) guideline.

The breakpoints for agents against *Enterobacteriaceae* were used to interpret tigecycline susceptibility against *Acinetobacter spp*. isolates (susceptible ≤ 2 μg/ml; intermediate 4 μg/ml; and resistant ≥ 8 μg/ml).[6,8-9] *Escherichia coli* ATCC® 25922 and *A. baumanii* ATCC® 19606 were provided as quality control isolates.[4,9-10]

**Results**

All *A. baumanii* isolates involved in this study were identified from patients hospitalised in intensive care and ward shown in **Table 1**. The clinical materials were sputum (500 samples), pus (67 samples), urine (61 samples), bronchial and pleural fluid (40 sample), blood (21 samples), cerebrospinal fluid (2 samples), and feces (1 sample). From all isolates, 78% came from lower respiratory tract, 9.86% from wound exudate (pus) and 8.82% from urine.

**Table 1.** General features of *A. baumanii* isolates from clinical specimen (n total = 692)

| Characteristics | N | % |
|---|---|---|
| Specimen source | | |
| Blood | 21 | 3.03 |
| Bronchial fluid | 34 | 4.91 |
| Cerebrospinal fluid | 2 | 0.29 |
| Feces | 1 | 0.15 |
| Pleural fluid | 6 | 0.87 |
| Pus | 67 | 9.68 |
| Sputum | 500 | 72.25 |
| Urine | 61 | 8.82 |
| Gender | | |
| Female | 264 | 38.15 |
| Male | 428 | 61.85 |
| Ward | | |
| Intensive care | 250 | 36.13 |
| Inpatient | 320 | 46.24 |
| Outpatient | 38 | 5.49 |
| Paediatric | 19 | 2.75 |
| Refferal from another hospital | 65 | 9.39 |

The frequency of *A. baumanii* was higher in year 2016. As the number of isolates of *A. baumanii* decreased from January – June 2016 period to July – December 2017, the tigecycline sensitivity against it increased for the same period (**Figure 1**).

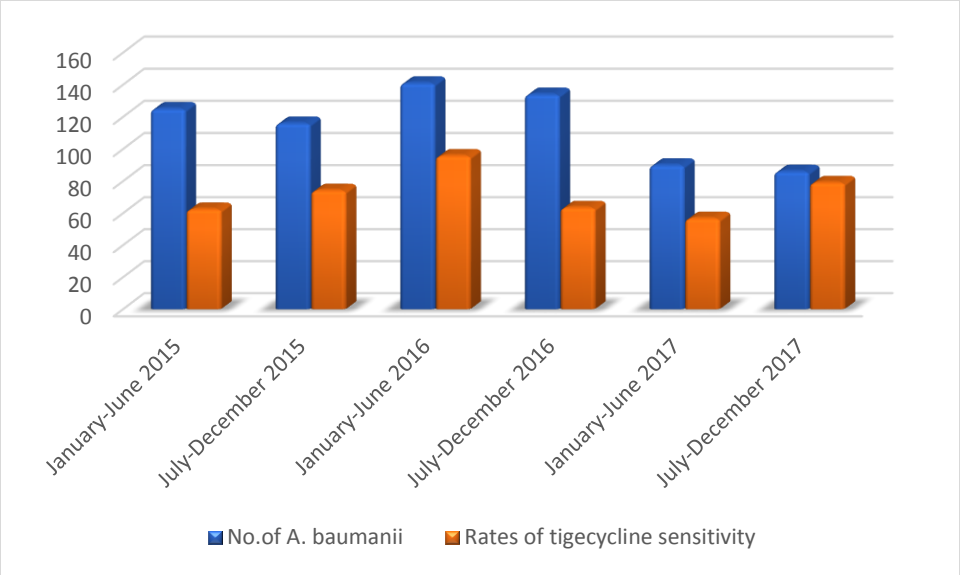


**Figure 1.** Number of isolates and tigecycline sensitivity against *A. Baumanii* from January 2015 – December 2017

From a total of 692 *A. baumanii* isolates, tigecycline MIC ranged from ≤ 0.5 to ≥ 8 µg/ml (Table 2.). Most of *A. baumanii* isolated in the study were multi-drug resistant with good susceptibility to tigecycline. Detailed result the activity of tigecycline were shown in Table 2, as well as Figure 1. This study identified 50.46% isolates had MIC ≤ 0.5 µg/ml, 2.38% with MIC = 1 µg/ml, and 19.07% with MIC = 2 µg/ml. The susceptibility rate for *A. baumanii* (MIC ≤ 2 µg/ml) were 68.27% in 2015, 79.58% in 2016, and 67.87% in 2017.

**Table 2.** In vitro activity of tigecycline against *A. baumanii* isolates

| | No. of isolates (%) | | | | | |
|---|---|---|---|---|---|---|
| | January-June 2015 | July-December 2015 | January-June 2016 | July-December 2016 | January-June 2017 | July-December 2017 |
| MIC range (µg/ml) | | | | | | |
| ≤ 0.5 | 36,80 | 42,24 | 95,74 | 43,28 | 28,89 | 55,81 |
| 1 | 3,20 | 2,59 | 0,00 | 1,49 | 0,00 | 6,98 |
| 2 | 22,40 | 29,31 | 0,00 | 18,66 | 27,78 | 16,28 |
| 4 | 30,40 | 24,14 | 0,00 | 28,36 | 23,33 | 13,95 |
| ≥ 8 | 7,20 | 1,72 | 4,26 | 8,20 | 20,00 | 6,98 |
| Susceptibility | | | | | | |
| Susceptible* | 62,40 | 74,14 | 95,74 | 63,43 | 56,67 | 79,07 |
| Intermediate** | 30,40 | 24,13 | 0,00 | 28,36 | 23,33 | 13,95 |
| Resistant*** | 7,20 | 1,72 | 4,26 | 8,21 | 20,00 | 6,99 |

## Discussion

*A. baumanii* has emerged especially in hospital evironment as one of the leading cause of nosocomial infection in immunocompromised patients. Resistance of this bacteria to numerous antibacterial agents, such as cephalosporins, aminoglycosides, fluoroquinolones, and carbapenems is an increasing problem globally.[7,9-10]

During the past decades, the incidence of multi-drug resistance *A. baumanii* particularly carbapenem-resistant has accounted for approximately 93% of reported infection in hospital setting.[11] Therefore, therapeutic options available for infected patients are limited, as the strain frequently exhibit high resistance to most existing antibiotics.[4,7,11-12]

Several studies from different geographical regions found that the prevalence of MDRAB infection/colonization varied from 17.2% to 92.89%.[1,10-14,] Thus, tigecycline is considered as the last option in the management of clinical infection caused by MDRAB.

Tigecycline MIC for *A. baumanii* in this study varied from ≤ 0.5 to ≥ 8 μg/ml, that was comparable with a study by Talaga K, et al. which found that ESBL-producing *A. baumanii*, likewise isolates non-carbapenemases, had the highest MIC level of 8.0 μg/ml; for AmpC-producing *A. baumanii* the highest MIC level was 6.0 μg/ml; and for MBL-producing isolates the MIC level was 2.0 μg/ml.[2] Since there was no reference MIC value for in vitro tigecycline susceptibility against *A. baumanii*, a suitable congruence of various tigecycline MIC value sensitivity test by Pieewngam and Kiratisin was used, with sensitive at MIC ≤ 0,5 and resistant at MIC > 2 μg/ml.[2,15] These values were different with EUCAST reference which MIC ≥ 1 μg/ml was regarded as resistant as these resistant strains do not have mutation that enables them to acquire resistance.[2]

The present study noted that tigecycline had a good in vitro activity against all isolates tested. This result is in contrast with a study from European country, where tigecycline showed activity of 50% or lower against MDRAB isolates.[6-7,16]

On the other side, previous studies conducted in other province in Indonesia and India revealed high susceptibility of tigecycline (75% and 82 - 88% respectively), although a sharp decline in the recent years has been marked.[1,10,12,17] Previous study by Chen et al detect a decreased susceptibility rate for *A. baumanii* (55.3% in 2009 and 73.4% in 2010).[17]

Almost all *A. baumanii* were obtained from respiratory tract of inpatients ward (78.03%). A study in other province in Indonesia demonstrated similar results, as 59.94% of *A. baumanii* were obtained in sputum, 0.9% in pleural fluid, and 0.3% in broncho alveolar lavage (BAL).[1] These results were in contrast with other studies such as a study by Dolma et al isolated 18.9% from sputum, a study by Villers et al isolated 24.8% from tracheo-bronchial specimens, and Suri et al isolated 45.6%.[1,18-19]

## Conclusion

As tigecycline demonstrated good value of MIC in this study, ranging between ≤ 0,5 to ≤ 2 μg/ml, it could be considered an effective antibiotic against *A. baumanii*, especially MDRAB. Due to the absence of bactericidal activity of tigecycline, these result must be interpreted cautiously before using tigecycline for infection due to MDR organisms, particularly MDRAB. The susceptibility rate of tigecycline against MDR isolates is alarming, thus wise consumption is warranted to prevent further increase of MDR organism.

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# Sensitivitas Dan Spesifitas Tes Provokatif Dan Pengukuran Latensi H Refleks Pada Sindrom Piriformis

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**ABSTRACT**

*Background* Piriformis syndrome (PS) is one causes of buttock and hip pain which is caused by pressure of sciatic nerves on piriformis muscle. PS is sometime misdiagnosed because of similar clinical signs and symptoms with other lower back pain diagnosis such as Hernia Nucleus Pulposus (HNP), Sacroiliac joint pain, facet joint pain. Gold standard diagnosis of PS is diagnostic block injection. However, provocative test and prolonged H reflex on EMG might be also standard diagnostic of PS.

*Aim* Understand the sensitivity and specificity of provocative test and prolonged H reflex to diagnose PS.

*Method* 72 patients with suspected PS who came to Neurology OPD in period of August- December 2017 were testing with physical examination (provocative test) and Electromyography test of H reflex. PS is diagnosed by positive diagnostic block injection. Data was proceeded with SPSS 20 version.

*Result* 72 patients with buttock pain which diagnosed with PS were dominated by female gender than male with ratio 1:3 with housewives as majority of work. Most age groups were 48.6% elderly (age more than 60 years old). Provocative tests result of Freiberg, FAIR, Beatty, Pace Sign, Hip Abduction sensitivity were 52.30; 66.15; 53.84; 46.15; 55.32 and specificity were 100; 42.85; 71.42; 71.42; 57.14. While sensitivity and specificity of prolonged H reflex more than 1.86 msec were 69.23 and 28.59. Combination of 3 provocative tests (FAIR, Freiberg and Beatty) resulted highest sensitivity and specificity in this study as 71.42 and 100.

*Conclusion* Provocative test and prolong H reflex can be supported diagnosis of PS. However both tests might not be comparable yet than diagnostic block injection as gold standard of PS. Combination of provocative test increased the sensitivity and specificity of provocative test than single test only.

***Keywords :*** **H reflex, piriformis syndrome, provocative test, sensitivity and specificity.**

**ABSTRAK**

*Latar belakang* Sindrom piriformis merupakan penyebab nyeri pada bokong dan tungkai bawah yang disebabkan oleh tertekannya nervus skiatika oleh otot piriformis. Diagnosis sindrom piriformis sulit ditegakkan karena gambaran klinis sindrom tersebut mempunyai kemiripan dengan HNP (*Hernia Nukleus Pulposus)*, nyeri sendi sakroiliaka maupun nyeri sendi faset. Sampai saat ini, alat diagnostik baku emas yang digunakan untuk diagnosis sindrom piriformis adalah injeksi blok diagnostik. Selain blok diagnostik, tes provokatif dan pemanjangan latensi H refleks pada pemeriksaan elektromiografi (EMG) dapat digunakan untuk menunjang diagnosis sindrom piriformis

*Tujuan* Mengetahui sensitivitas dan spesifisitas tes provokatif dan pemanjangan H refleks pada sindrom piriformis

*Metode* Subjek penelitian adalah 72 pasien sindrom piriformis yang datang ke poli saraf SHLV dalam rentang waktu Agustus-Desember 2017. Pada subjek penelitian tersebut dilakukan pemeriksaan fisik berupa tes provokatif dan pemeriksaan EMG (Elektromiografi) untuk mengukur delta H refleks. Sindrom piriformis ditegakkan dengan blok diagnostic positif. Studi menggunakan desain tes diagnostik. Data dikumpulkan dan dianalisis menggunakan SPSS versi 20.

*Hasil* Sebanyak 72 pasien yang mengalami keluhan pada area bokong dan terdiagnosis Sindrom Piriformis, rasio antara pria dan wanita sebesar 1:3. Usia terbanyak didapatkan pada kelompok usia >60 tahun sebanyak 48.6% dengan riwayat pekerjaan terbanyak adalah ibu rumah tangga. Tes provokatif berupa Freiberg, FAIR, Beatty, Pace Sign, Hip Abduction berturut-turut menghasilkan sensitivitas sebesar 52.30; 66.15; 53.84; 46.15; 55.32 dan spesifitas sebesar 100; 42.85; 71.42; 71.42; 57.14. Sedangkan untuk pemanjangan delta H refleks lebih sama dengan 1.86 memiliki sensitivitas

sebesar 69.23 dengan sensitivitas sebesar 28.59. Kombinasi tes provokatif FAIR, Freiberg, beatty menghasilkan sensitivitas dan spesifitas terbesar dalam studi ini sebesar 71.42 dan 100%.
*Kesimpulan* Tes provokatif dan pengukuran delta H reflex pada EMG dapat digunakan sebagai diagnosis penunjang sindrom piriformis. Namun sensitivitas dan spesifitas kedua tes tersebut masing-masing masih belum sebanding dengan tes diagnostik blok injeksi m.piriformis. Kombinasi dari tes provokatif meningkatkan sensitivitas dan spesifitas.

***Kata Kunci :*** **H reflex, Sensitivitas dan spesifitas, Sindrom Piriformis, Tes provokatif.**

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## Pendahuluan

Sindrom piriformis adalah sindrom neuritis perifer saraf skiatika yang disebabkan oleh kondisi abnormal otot piriformis seperti hipertrofi, inflamasi, ataupun variasi anatomik sehingga menghasilkan iritasi dan penjepitan pada saraf skiatika. Otot piriformis yang terletak di bawah otot gluteus maksimus mengalami spasme sehingga menekan saraf skiatika yang berada didekatnya dan mengakibatkan nyeri dan rasa baal di sepanjang tungkai bawah bagian belakang sampai ke kaki.[1] Sindrom piriformis terutama didapati pada usia dekade 4 hingga 5, yang umumnya terjadi pada wanita, dengan rasio perbandingan wanita dan pria 6:1. Hasil tersebut didapat dari sekitar 6% pasien dengan keluhan nyeri punggung bawah yang terdiagnosis sebagai sindrom piriformis. Angka prevalensi dari sindrom piriformis tidak diketahui dengan pasti namun diperkirakan berkisar 5-36%.[2] Sindrom piriformis memiliki variasi dua tipe, yaitu primer dan sekunder: Sindrom piriformis primer berkaitan dengan letak anatomis otot piriformis dan saraf skiatika. Sindrom piriformis primer terjadi pada 15% kasus dengan diagnosis sindrom piriformis. Sindrom piriformis sekunder disebabkan oleh mikrotrauma, makrotrauma, dan iskemik lokal.[2]

Dalam praktek sehari-hari diagnosis sindrom piriformis ditegakkan oleh klinisi melalui anamnesa, pemeriksaan fisik, dan pemeriksaan penunjang. Namun diagnosis sindrom piriformis sulit ditegakkan karena gambaran klinis sindrom tersebut mempunyai kemiripan dengan beberapa penyebab nyeri pinggang lainnya, seperti misalnya HNP (*Hernia Nukleus Pulposus)*, nyeri sendi sakroiliaka maupun nyeri sendi faset. Pemeriksaan penunjang seperti X-Ray, ultrasonografi (USG) maupun MRI (*Magnetic Resonance Imaging*) hanya digunakan untuk menyingkirkan penyebab lainnya dan tidak dapat digunakan untuk menyatakan diagnosis suatu sindrom piriformis.

Salah satu cara untuk mendiagnosis sindrom piriformis adalah dengan diagnostik blok injeksi pada otot piriformis, tetapi karena prosedur suntikan tersebut memerlukan keterampilan dan kompetensi penggunaan USG maupun fluoroskopi maka prosedur tersebut jarang dilakukan terutama pada rumah sakit yang tidak memiliki fasilitas USG maupun fluoroskopi. Karena tidak adanya suatu pemeriksaan penunjang radiologi yang dapat dengan tegas mendiagnosis sindrom piriformis, seringkali klinisi menggunakan tes provokatif yang digunakan untuk mendukung suatu diagnosis sindrom piriformis. Selain pemeriksaan klinis tes provokatif, pemeriksaan penunjang *Electromyography* (EMG) dapat mendukung diagnostik sindrom piriformis. Oleh karena belum banyak data penelitian yang mendukung tes provokasi dan EMG tersebut, penulis tertarik meneliti mengenai senstivitas dan spesifitas tes provokatif dan latensi H refleks pada pemeriksaan EMG untuk mendeteksi sindrom piriformis.

## Bahan Dan Metode

Sampel penelitian adalah pasien poliklinik saraf Rumah Sakit Siloam yang datang dengan keluhan nyeri bokong yang menjalar dengan skala nyeri ≥7 dalam rentang waktu Agustus – Desember 2017. Pasien dilakukan wawancara dan pemeriksaan fisik (tes provokatif) berupa *Freiberg, FAIR, Beatty, Pace Sign*, dan *Hip Abduction* serta pemeriksaan EMG berupa pengukuran delta H refleks peroneus.

*Freiberg's manuver* merupakan gerakan memutar yang dilakukan secara hati-hati pada tungkai bawah ketika pasien dalam keadaan berbaring dengan mencoba melakukan peregangan yang dapat mengiritasi piriformis dan memprovokasi penekanan pada nervus skiatik.

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*Pace maneuver* memunculkan rasa nyeri dengan melakukan abduksi pada pinggul saat pasien dalam posisi duduk. Hal ini lebih dapat mengaktivasi piriformis daripada dengan melakukan peregangan. *Beatty* dilakukan dengan abduksi pada paha dengan lutut yang difleksikan, lalu tungkai diangkat keatas. FAIR test (*Flexion adduction internal rotation*), yang dikatakan positif bila terasa nyeri saat fleksi, aduksi dan internal rotasi pada pinggul dengan fleksi lutut. *Hip abduction test* dilakukan dengan meminta pasien berbaring pada satu posisi kemudian diminta untuk mengabduksi panggul (posisi badan tegak) sekitar 45° dengan penguji mengamati gerakan dan nyeri yang timbul saat gerakan dilakukan.

Sesudah dilakukan maneuver tes provokatif, dicatat apakah pasien mengalami nyeri yang dicetuskan oleh maneuver tesebut. Setelah maneuver, pasien dilakukan pemeriksaan EMG untuk menilai pemanjangan refleks H peroneus. Kemudian pasien dilakukan blok diagnostik yakni injeksi otot piriformis dengan lidokain dan/ atau kortikosteroid oleh dokter spesialis saraf dengan penunjang USG. Diagnosa sindrom piriformis ditegakkan apabila pasien mengalami penurunan derajat nyeri sebesar 75% paskainjeksi dibandingkan dengan skala nyeri sebelum injeksi. Pasien dengan riwayat autoimun dalam keluarga dan memiliki kelainan pada foto polos pelvis dieksklusi dalam penelitian ini. Penelitian ini merupakan studi desain tes diagnostik dengan menggunakan teknik konsekutif sampling yang diolah menggunakan SPSS versi 20. Nilai sensitivitas dan spesifisias dihitung dengan menggunakan rumus sebagai berikut: sensitivitas = a/ a+c dan spesifitas = d/b+d dengan keterangan berupa a:*true positive*; b:*false positive*; c:*false negative*; d:*true negative.*

## Hasil

Sebanyak 72 pasien yang mengalami keluhan pada area bokong dan terdiagnosis sindrom piriformis, rasio antara pria dan wanita sebesar 1:3 dengan riwayat pekerjaan sebesar 54.2% untuk ibu rumah tangga. Usia terbanyak pada kelompok usia >60 tahun sebanyak 48.6% (Tabel 1). Tes provokatif berupa Freiberg, FAIR, Beatty, Pace Sign, Hip Abduction berturut-turut menghasilkan sensitivitas sebesar 52.30; 66.15; 53.84; 46.15; 55.32 dan spesifitas sebesar 100; 42.85; 71.42; 71.42; 57.14. Sedangkan untuk pemanjangan delta H refleks lebih sama dengan 1.86 memiliki sensitivitas sebesar 69.23 dengan sensitivitas sebesar 28.57. Dua atau lebih tes provokasi yang dilakukan menghasilkan senstivitas dan speseifitas yang lebih tinggi dibandingkan dengan satu jenis tes provokasi saja. Tes provokasi FAIR, Freiberg, dan Beatty merupakan kombinasi tes provokasi yang memiliki sensitivitas dan spesifitas tertinggi dalam studi ini sebesar 71.42% dan 100% (Tabel 2).

**Tabel 1.** Karakteristik Demografik

| **Kelompok Usia** | **Frekuensi (n)** | **Persentase (%)** |
|---|---|---|
| 20-39 | 4 | 5.6 |
| 40-49 | 12 | 16.7 |
| 50-59 | 21 | 29.2 |
| >60 | 35 | 48.6 |
| **Jenis Kelamin** | | |
| Pria | 18 | 25 |
| Wanita | 54 | 75 |
| **Riwayat Pekerjaan** | | |
| Tidak bekerja | 1 | 1.4 |
| Ibu Rumah Tangga | 39 | 54.2 |
| Pekerja Kantor | 9 | 12.5 |
| Pekerja Lapangan | 23 | 31.9 |

**Tabel 2.** Tes Diagnostik

| Tes Diagnostik | Sensitivitas (%) | Spesifisitas (%) |
|---|---|---|
| Freiberg | 52.30 | 100 |
| FAIR | 66.15 | 42.85 |
| Beatty | 53.84 | 71.42 |
| Pace | 46.15 | 71.42 |
| Hip abduction | 55.32 | 57.14 |
| FAIR & Freiberg | 64.51 | 100 |
| FAIR & Beatty | 61.90 | 75 |
| FAIR, Freiberg, Beatty | 71.42 | 100 |
| FAIR, Freiberg, Pace | 66.67 | 100 |
| Delta H reflex (≥1.86) | 69.23 | 28.57 |

## Pembahasan

Prevalensi terjadinya sindrom piriformis masih sangat bervariasi dengan rentang 5-36% dari kasus nyeri pinggang tergantung dengan kriteria diagnosis yang digunakan. Sindrom tersebut umumnya terjadi pada rentang usia 40-60 tahun dan didapat pada individu dengan berbagai macam aktifitas dan pekerjaan. Hopayian dkk (2010) melaporkan usia rata rata penderita sindrom piriformis pada masing masing penelitiannya adalah 43 tahun. Namun demikian, beberapa penelitian terbaru menunjukkan pergeseran onset terjadinya sindrom piriformis pada rentang usia 30–40 tahun seperti yang dilaporkan oleh Mondal dkk (2017) yang melaporkan rata rata usia penderita sindrom tersebut adalah 32,3 tahun. Laporan tersebut mendukung penelitian sebelumnya oleh Jawish dkk (2010) dan Danilo dkk (2013) yang menyebutkan rata rata usia penderita adalah 35,37 tahun dan 38 tahun. Dibandingkan beberapa penelitian diatas, terdapat hasil yang berbeda dimana didapatkan usia penderita >60 tahun menjadi kelompok dengan proporsi terbesar (47%) diikuti oleh kelompok usia 50-59 tahun (29%) sedangkan pada kelompok usia 20-39 tahun, sindrom tersebut hanya diderita oleh 6,2% penderita.

Penelitian sebelumnya telah menunjukkan bahwa wanita lebih banyak menderita sindrom piriformis dibanding pria walaupun dengan perbandingan yang bervariasi, Danilo dkk (2013) menemukan rasio wanita dibandingkan pria 6:1, Chen dkk (2012)[6] melaporkan rasio sebesar 3:2. Hasil penelitian inipun menunjukan jenis kelamin wanita lebih banyak dibandingkan pria dengan rasio 3:1. Predisposisi wanita lebih besar pada sindrom piriformis diduga terkait dengan struktur anatomi dari sudut otot quadriceps femooris pada os coxae (pelvis) wanita lebih lebar dibandingkan pria.[4] Studi lain menuliskan perubahan hormonal pada wanita terutama selama kehamilan juga dapat mempengaruhi terjadinya sindrom piriformis.[8]

Diagnosis sindrom piriformis saat ini sangat mengandalkan pemeriksaan klinis sementara neuroimaging belum dapat menentukan apakah telah terjadi proses inflamasi atau kompresi pada otot piriformis selama terjadinya sindrom.

Beberapa tes klinis maupun pemeriksaan penunjang telah digunakan untuk membantu mendiagnosis sindrom piriformis. Seperti misalnya Pace dan Nagle (1976) menggunakan tes provokatif Pace dan Freiberg pada pasien yang mengalami nyeri pinggang dan melaporkan 6% dari 750 pasien tersebut terdiagnosis sindrom piriformis, demikian juga Benson dan Schutzer yang dengan menggunakan tes FAIR melaporkan 15% dari 93 penderita nyeri skiatika didiagnosis sebagai sindrom piriformis. Namun hingga saat ini tidak terdapat satupun kriteria diagnosis yang baku dalam mendiagnosis sindrom piriformis. Hal ini mungkin dikarenakan belum adanya pemeriksaan dengan trial kontrol yang dapat diandalkan.[10]

Tes provokatif merupakan tes klinis yang mudah dilakukan oleh setiap klinisi tanpa memerlukan keahlian ataupun alat tertentu dengan waktu pemeriksaan yang singkat. Tes terebut bertujuan meregangkan otot piriformis yang teriritasi dan memprovokasi terjadinya kompresi saraf siatika Beberapa jenis tes provokasi yang telah dilakukan dalam beberapa studi untuk menegakkan diagnosis sindrom piriformis adalah tes FAIR (*Flexion adduction internal rotation*), Freiberg, Pace, Beatty, Hip Abduction, Lasegue, manuver HCLK (*Heel-contralateral knee*), dan Hughes.

Tes-tes tersebut dapat digunakan sebagai alat tes diagnostik untuk mendeteksi sindrom piriformis. Meskipun jarang diterapkan dalam praktek sehari hari pemeriksaan penunjang EMG (*electromyography)* telah digunakan oleh beberapa senter sebagai pemeriksaan penunjang diaagnosa sindrom piriformis. Berbeda dengan tes provokatif, tes ini memerlukan peralatan yang mahal, operator yang terlatih serta ruangan yang memadai. Penelitian ini dilakukan untuk mengetahui sensitivitas dan spesifisitas tes provokatif Freiberg, FAIR, Beatty, Pace, Hip abduction dan EMG dalam mendiagnosis sindrom piriformis.

Tes FAIR merupakan salah satu tes provokatif dengan sensitivitas tertinggi. Fishman dkk melaporkan FAIR memiliki sensitivitas dan spesifisitas sebesar 88,1 dan 83,2. Pada penelitian ini, nilai sensitivitas tes FAIR sebesar 66.15% dan merupakan tes provokatif dengan nilai sensitivitas tertinggi. Namun nilai spesifitas dari tes ini justru terkecil dibandingkan tes provokatif lainnya yakni sebesar 42.85%.

Tes Freiberg bertujuan memunculkan rasa nyeri pada area trochanterika saat dilakukan rotasi internal pasif dari panggul. Tes ini memiliki kelemahan yakni menghasilkan nyeri pinggang dan kaki pada penelitian terhadap 100 pasien pasien dengan HNP lumbal, demikian pula pada penelitian 27 pasien dengan gangguan abnormalitas sendi lipat paha. Pada studi ini, kami mendapatkan angka sensitivitas dan spesifitas Freiberg sebesar 52.30% dan 100%. Hasil penelitian tersebut tidak dapat dibandingkan dengan penelitian lainnya karena belum didapat data hasil penelitian yang menilai sensitifitas dan spesifisitas tes ini.

Pace atau *active piriformis test* dilakukan dengan melakukan gerakan abduksi pada panggul saat pasien dalam posisi duduk, dan dianggap positif apabila pasien mengalami nyeri. Pada penelitian ini didapat sensitifitas dan spesifisitas tes Pace sebesar 46,15% dan 71,42 %, hasil tersebut berbeda dengan yang dilaporkan oleh Martin (2013) menuliskan sensitivitas dan spesifitas tes Pace sebesar 78% dan 90%.

Tes Beatty merupakan salah satu tes provokatif yang sensitif terhadap sindrom piriformis Gerakan abduksi pada tes ini menyebabkan nyeri pada bokong bagian dalam yang menandakan iritasi saraf skiatika. Sensitivitas uji ini sebesar 53.84% dengan spesifitas sebesar 71.42%. Sedangkan tes *Hip abduction* atau gerakan abduksi panggul menghasilkan nilai sebesar 55.32 dan 57.14.
Abnormalitas hip abduction dapat diakibatkan pemendekan otot piriformis ataupun overaktivitas dari otot quadratus sehingga menghasilkan sindrom piriformis. Pada studi lain, sensitivitas dan spesifitas kedua uji ini belum pernah dilakukan.

Pemeriksaan elektrodiagnostik memiliki kemampuan untuk membedakan kondisi piriformis dengan kondisi lainnya. Saraf terjepit menghasilkan abnormalitas EMG seperti kelemahan otot dan atrofi dari otot distal dan proksimal dari piriformis, sedangkan sindrom piriformis menunjukkan kelemahan dan atrofi hanya pada bagian distal. Evaluasi ini dapat menandakan denervasi otot yang dipersarafi n.skiatika. H refleks dapat saja memanjang atau tidak muncul pada anggota gerak bawah yang terkena. Fishman menyimpulkan pemanjangan latensi H refleks sebesar 1.86 msec saat adduksi dan fleksi panggul diduga sebagai sindrom piriformis.[11]

Sedangkan untuk pemanjangan delta H refleks sama dengan 1.86 memiliki sensitivitas sebesar 69.23 dengan sensitivitas sebesar 28.57. Secara keseluruhan hasil sensitivitas dan spesifitas pada masing-masing tes provokasi dan pemanjangan H refleks masih belum bermakna dibandingkan spesifitas dan senstivitas dari kombinasi tes provokasi dengan atau tanpa pemeriksaan H refleks.

Kombinasi terbesar didapat pada kombinasi pemeriksaan FAIR, Freiberg, dan Beatty dengan sensitivitas dan spesifitas sebesar 71.42 dan 100. Oleh karena itu disimpulkan kombinasi tes provokasi dan/ pengukuran H refleks lebih bermakna dibandingkan satu pemeriksaan saja, karenanya setiap klinisi diharapkan melakukan pemeriksaan secara komperhensif. Keterbatasan dalam penelitian berupa jumlah sampel penelitian masih terbilang kecil dikarenakan studi berupa konsekutif sampling. Selain itu, penentuan senstifitas dan spesifitas pada pemeriksaan tes provokatif terbatas hanya pada 5 jenis pemeriksaan yang paling sering digunakan saja, sehingga tidak seluruh pemeriksaan provokatif dilakukan

## KESIMPULAN

Tes provokatif dan pengukuran delta H reflex pada EMG dapat digunakan sebagai diagnosis penunjang sindrom piriformis.

Sensitivitas dan spesifitas kedua tes tersebut masing-masing masih belum sebanding dengan tes diagnostik blok injeksi m.piriformis. Namun kombinasi dari 2 atau lebih tes provokatif memiliki sensitivitas dan spesifitas yang lebih tinggi.

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# A Planned Cesarean Section-Hysterectomy for Placenta Previa Totalis Percreta in Patient with History of Two Cesarean Sections

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**Abstract**

The presence of placenta previa may be associated with placenta accreta[1]. Maternal and fetal morbidity and mortality from placenta previa accreta are considerable and are associated with high demands on health resources. With the rising incidence of caesarean sections combined with increasing maternal age, the number of cases of placenta praevia and its complications, including placenta accreta, will continue to increase[2]. Here, we present a case of placenta previa totalis percreta in previous cesarean section twice. In this case, patient with placenta previa totalis-percreta we diagnosed and prepared proper management with the involvement of multidisciplinary team. We reduced blood loss by performing total abdominal hysterectomy immediately after delivered the baby and the postoperative course was uneventful.

**Keywords:** *Cesarean Section-Hysterectomy, placenta accreta, placenta percreta, placenta previa*

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## Introduction

Placenta previa may be associated with placenta accreta[1]. *Placenta accreta* is a general term used to describe the clinical condition when part of the placenta, or the entire placenta, invades and is inseparable from the uterine wall[2] [3] . Such abnormally firm attachment of the placenta might be anticipated because of poorly developed decidua in the lower uterine segment. Placenta percreta is one of the most serious complications of placenta accreta that penetrates the myometrium of the uterine wall.

It is a life threatening condition, frequently associated with severe obstetric hemorrhage blood transfusions and a cesarean hysterectomyusually necessitating for to control the significant blood loss.

The maternal and fetal morbidity and mortality from placenta accreta are considerable and associated with high demands on health resources[2] [3]. A positive correlation can be seen between the incidence of placenta accreta and the rising rate of caesarean section[2] [4]. Damage to the uterus created by surgery leaves patients susceptible to the acquisition of future placenta accreta.

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The occurrence of placenta previa, uterine scarring and increased maternal age are risk factors in contributing to the incidence of placenta accreta and this ultimately poses a significant burden on health resources. A multidisciplinary approach is necessary in managing this serious complication[4]. We present a case of placenta previa percreta diagnosed by ultrasound, in which we accomplished a well planned cesarean section-placenta left in situ-hysterectomy.

## Case

A 41-year-old (gravida 3, para 2) on her 35 weeks of gestation came for the first time to the our outpatient department in Siloam public hospital for prenatal check-up. The patient had previous prenatal check-up in a clinic with midwife without ultrasound examination. She had two previous cesarean section due to dysfunctional labor arrest in cervical dilatation. She denied any history of vaginal bleeding. 2D-ultrasound performed, revealed an alive single intrauterine pregnancy in transverse lie position, biometry appropriate to 35 weeks of gestation with adequate amniotic fluid, normal fetal heart tone 146 beats per minute. The placenta totally covered the cervix, suspected placenta accreta. Patient had never experienced vaginal bleeding.

Patient then referred to the Maternal-Fetal Medicine Department for confirmation of the placenta accreta.

The ultrasound and color-Doppler examination confirmed the placenta previa totalis accreta-percreta.

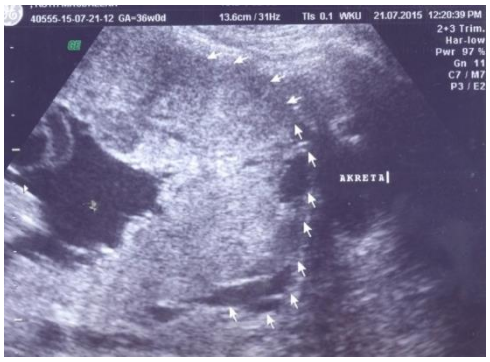


Figure 1.
2D transabdominal ultrasound showed the absence of placental- miometral interface, the uterine wall is undistinguishable from the placenta, and the presence of multiple vascular intraplacental lacunae “Swiss cheese” placental appearance

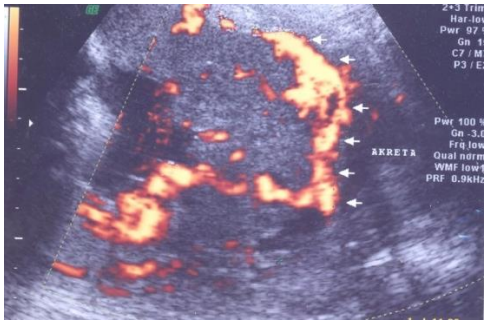


Figure 2.
2D color Doppler ultrasound revealed an extensive vascularity along the anterior portion of the lower uterine segment and appeared to extend up to and around the bladder

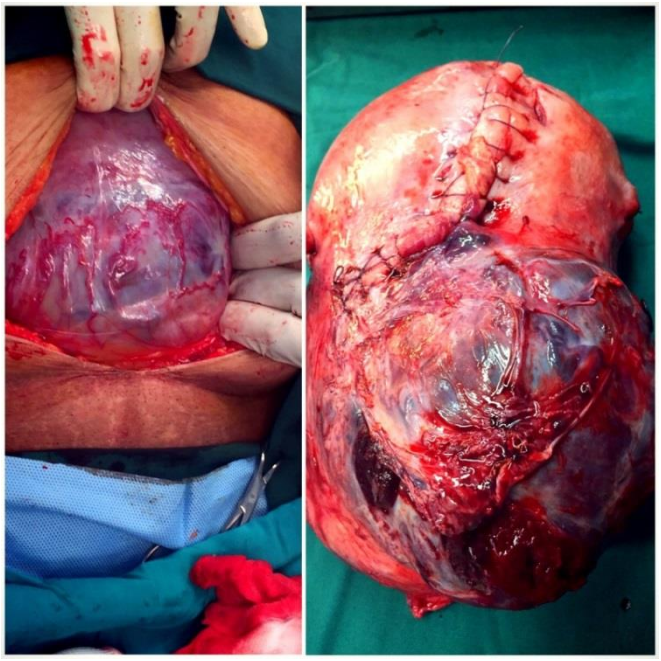

Figure 3.
(Left) – On exploration, the black arrow showed placenta percreta, chorionic villi penetrate the full thickness of the myometrium and invade the bladder.
(Right) – After surgery-total abdominal hysterectomy, the uterus with placenta in situ.

**Discussion**

The incidence of placenta accreta has increased and seems to parallel the increasing cesarean delivery rate. Researchers have reported the incidence of placenta accreta as 1 in 533 pregnancies for the period of 1982–2002[2]. This contrasts sharply with previous reports, which ranged from 1 in 4,027 pregnancies in the 1970s, increasing to 1 in 2,510 pregnancies in the 1980s [3]. Placenta previa may be associated with placenta accreta[1]. Placenta accreta is classified according to its degree of invasion into the myometrium : placenta accreta, placenta increta, and placenta percreta. *Placenta accreta* is a term used to denote a placenta with villi that adhere to the superficial myometrium. *Placenta increta* This maneuver causes massive hemorrhage that is often quite challenging to control. A firm preoperative diagnosis allows adequate preparation and organization of multidisciplinary help for what may be a difficult surgical procedure requiring massive blood transfusion[6].

First line imaging modalities for the diagnosis of placenta accreta include gray-scale ultrasound (2D ultrasound) and color Doppler. MRI is used as an adjunct tool to improve sensitivity when sonographic examination is equivocal or when the placenta cannot be reliably visualized[7].

occurs when the villi adhere to the body of the myometrium, but not through its full thickness. *Placenta percreta* occurs when the villi penetrate the full thickness of the myometrium and may invade neighboring organs such as the bladder or the rectum[5]. Predisposing factors other than previous caesarean sections include all previous myometrial damage from myomectomy, manual removal of the placenta, complicated uterine curettage, and leiomyomas[3]. Bladder invasion by the placenta percreta is a potentially life-threatening obstetric complication, albeit a rare one. The diagnosis is usually established when attempts are made to separate the adherent placenta from the bladder.

Overall, gray scale ultrasonography is sufficient to diagnose placenta accreta, with a sensitivity of 77–87%, specificity of 96–98%, a positive predictive value of 65–93%, and a negative predictive value of 98 [3]. The use of power Doppler, color Doppler, or 3D imaging does not significantly improve the diagnostic sensitivity compared with that achieved by gray scale ultrasonography alone [2]. The 2D ultrasound criteria for the diagnosis of placenta accreta in at-risk patients are obliteration of the retroplacental echolucent zone, abnormal prominent placental lacunae and thinning or disruption of the

hyperechoic uterine serosa–bladder interface [8]. These lacunae may result in the placenta having a "moth-eaten" or "Swiss cheese" appearance [3], as seen in Figure 1.

The value of diagnosing placenta accreta before delivery is to maximize planning and assemble a multidisciplinary team. Ideally when delivering, there should be a Consultant grade Obstetric surgeon and anesthetist. If possible input from pelvic surgeon such as a gynecologic oncologist, maternal–fetal medicine specialist, neonatologist, urologist, vascular surgeon, and interventional radiologist should be included to optimize the patient's outcome[3]. There are a many considerations for management depending on the severity of hemorrhage, including life-saving hysterectomy. Ensuring sufficient blood for transfusion and early transfer to a tertiary care center must be considered. There is some controversy regarding the benefit of interventional radiology with balloon catheterization to reduce blood loss[9]. Postpartum hemorrhage and maternal mortality are of such high risk in these patients that proper diagnosis and planning is the key to improved-outcomes.

In this case, with a proper diagnosis and well planned management, we can prevent a large amount of blood loss. A proper diagnosis of placenta accreta is highly recommended when physicians find patient with placenta previa and histories of cesarean section. The value of ultrasound is very important and further imaging modalities such as MRI to assist in making the accurate diagnosis in high risk patients with previous uterine scars, together with appropriate training and multidisciplinary input to improve patient outcomes.

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# Anesthetic Challenges for Modified Bentall Procedure in a Pregnant Marfan Patient with Acute Stanford Type A Dissection

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***Abstract***

*Aortic dissection is a life-threatening condition which requires immediate surgical intervention. It has been estimated that half of aortic dissection and/or ruptures in women younger than 40 years of age have been associated with pregnancy.[19] The limited data on the coincidence of Marfan syndrome, pregnancy and aortic dissection makes its anesthetic management a formidable challenge to any anesthesiologist.*

*This is a case of a 33-year-old G1P0, 28 weeks age of gestation with Marfan syndrome, who had Aortic Dissection Stanford type A and underwent an emergency Modified Bentall's surgery with cardiopulmonary bypass and deep hypothermic circulatory arrest.*

*This case illustrates the dilemma of managing this case since there are two patients involved, mother and fetus. Wrong decision could result in demise of both. Although the aim is life for both, survival of one without neurologic sequelae is already considered a success.*

***Keywords: Marfan syndrome, Modified Bentall Procedure, Pregnancy, Acute type A dissection***

**Abstrak**

Diseksi aorta adalah kondisi yang mengancam jiwa yang memerlukan intervensi bedah segera. Diperkirakan bahwa setengah kasus dari diseksi aorta dan / atau ruptur aorta pada wanita yang lebih muda dari 40 tahun berhubungan erat dengan kehamilan. 19 Keterbatasan data mengenai manajemen anestesi pada pasien hamil dengan sindrom Marfan yang mengalami diseksi aorta merupakan tantangan tersendiri pada seorang ahli anestesi .

Berikut ini adalah laporan kasus seorang pasien hamil G1P0 berusia 33 tahun, usia kehamilan 28 minggu dengan sindrom Marfan, yang memiliki Diseksi aorta Stanford tipe A dan menjalani operasi darurat Bentall's Modifikasi dengan *bypass* kardiopulmonari dan *deep hypothermic circulatory arrest*. Laporan ini menggambarkan dilema yang timbul dalam pengelolaan kasus dimana terdapat dua pasien yang terlibat, ibu dan janin. Keputusan yang salah bisa mengakibatkan kematian keduanya. Meskipun tujuannya adalah untuk kelangsungan hidup ibu dan janin, kelangsungan hidup salah satu pasien tanpa gejala sisa neurologis merupakan suatu keberhasilan.

**Kata kunci : sindroma marfan, Prosedur Bentall, Kehamilan, Diseksi aorta tipe A akut**

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## Introduction

Acute aortic dissection of the ascending aorta (Stanford type A) is highly lethal. Forty percent of patients who reach the emergency department die immediately. This mortality rate is increased by 1% per hour in the first 48 hours and between 5%-20% die during or shortly after the surgery.[2,24,32]

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Early death may occur as a result of malperfusion syndromes (cerebrovascular, visceral, renal, or peripheral ischemia), cardiac complications (acute aortic insufficiency, coronary ischemia, cardiac tamponade), or free rupture.[17] Surgery, which aims to prevent aortic rupture, cardiac complications and other end-organs damage, is the definitive treatment for patient with type A acute aortic dissection.

Deep hypothermic circulatory arrest (DHCA) is technique required in cases of acute aortic dissection or aneurysms that extend into the aortic arch.[49]

Surgical replacement of the aortic valve and surgery of the aortic aneurysm or dissection that extend into the aortic arch carry risk of neurologic injury from global ischemia or embolization of atherosclerotic debris secondary to clamping of the great vessels.[5] Surgery of descending aorta is associated with postoperative paraplegia secondary to interruption of 13 to 17% of blood supply of the spinal cord.[5]

This case report will show how neurologic sequelae was prevented during anesthesia for modified Bentall procedure to a pregnant Marfan patient with acute type A dissection.

### *Case summary*

This is a case of a 33-year-old primigravid, 28 weeks age of gestation (AOG) with Marfan syndrome, who consulted due to sudden chest discomfort with radiation to the left jaw associated with burning substernal chest pain and diaphoresis.

Past medical history showed that the patient had hiatal hernia and gastroesophageal reflux disease (GERD) and was on esomeprazole tab as needed. She had no previous surgery. Prenatal check up was not clear.

Family history showed that her mother and brother have Marfanoid features. Physical examination revealed a conscious, coherent patient who arrived via stretcher. She weighs 60 kg and stands160 cm. Her vital signs were as follows: blood pressure (BP) 106/69 mmHg on both upper extremities, 110/71 on both lower extremities, heart rate (HR) 97-100 bpm, respiratory rate (RR) 20 per minute. Airway examination revealed mallampati I classification with good neck movement. Chest examination revealed a pectus carinatum deformity. Her abdomen was globular. Fetal heart tone was appreciated at 150 beats per minute. Cephalic presentation was palpable. No uterine contractions were noted. Internal examination revealed a soft and close cervix. Her arm span of 174 cm with positive wrist and thumb sign were noted. Hindfoot deformity was also observed. Good peripheral pulses were appreciated. Neurologic examination revealed intact cranial nerves, normal motor strength, no tingling nor numbness, normal response of tendon reflexes with no pathologic reflexes found.

Diagnostic workups revealed anemia with leucocytosis, neutrocytosis and hypocalcemia (see Appendix A). Carotid duplex scan showed > 50% stenosis in the left common carotid artery. Positive troponin I indicates myocardial necrosis. Transesophageal echocardiography (TEE) showed a hypocontractile free walls of the right ventricle. An echocardiography showed aortic dissection confirmed by magnetic resonance angiography (MRA) which showed aortic dissection Stanford type A (Fig. 1A & 1B).

Patient was diagnosed to have aortic aneurysm and dissection Stanford type A with carotid stenosis and right coronary artery disease, Marfan syndrome, G1P0 28 weeks AOG cephalic, not in labor. She was classified as ASA class III-E.

Modified Bentall's procedure with double set up for possible obstetrical intervention was contemplated. Risks and benefits were explained to patient and relatives. The risk of demise for both the patient and fetus was not eliminated. Survival of patient but with neurologic and nephrologic sequelae was also a possibility. There was no immediate indication for an emergency caesarian section and fetal demise can occur. The risks were explained by all specialists — obstetrician, cardiologist, thoracic, cardiovascular surgeon, intensivist, neonatologist and anesthesiologist. Patient and relatives accepted risks. Urgent modified Bentall procedure was scheduled.

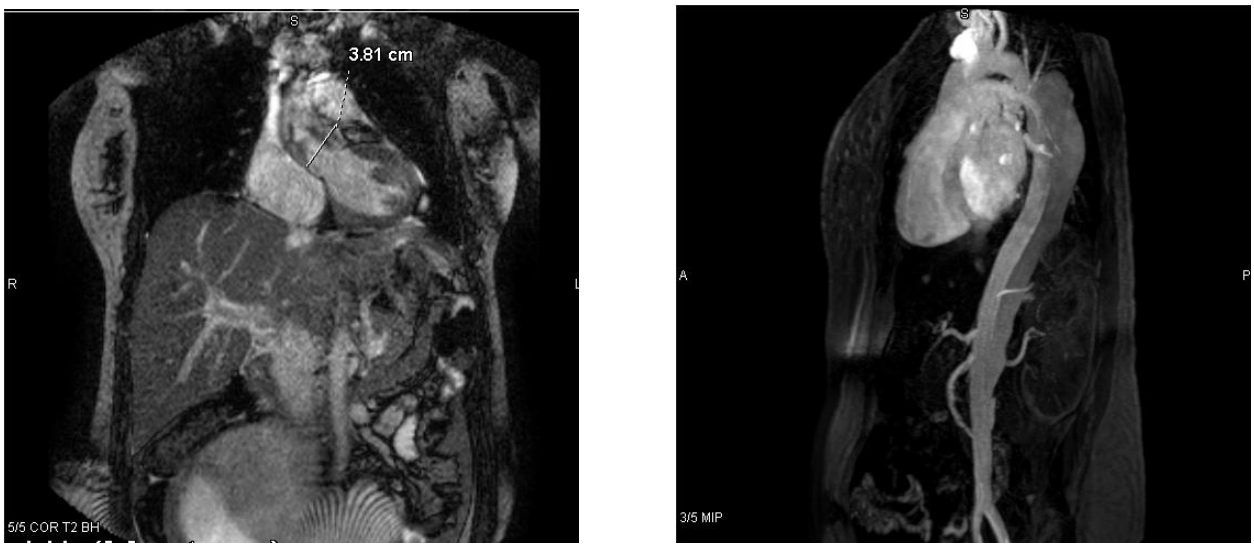


**Figure 1A&B.** MRA of the chest/thoracic (9/29/10) showed aortic aneurysm with dissection at the level of proximal ascending aorta down to the visualized common iliac arteries.

Patient was given betamethasone 12 mg IM and cefuroxime IV prior to the surgery. Packed RBC, thawed fresh frozen plasma, platelet concentrate and fresh whole blood were prepared for use Monitors placed were as follows: temperature probe on the nasopharynx, 5 leads-ECG, end tidal CO2, arterial line at right radial artery and left brachial artery, and pulmonary artery catheter inserted in the right internal jugular vein. Urethral catheter was inserted to monitor the urine output hourly.

Initial vital signs were as follows: BP 165/60 mmHg, HR 105 bpm and pulmonary arterial pressure (PAP) 25/19 mmHg (normal PAP is 15-28/ 5-16mm Hg).[52]

Initial arterial blood gas showed a metabolic acidosis (see Appendix A) and was corrected with the NaHCO3 administration. Nitroglycerin drip was started during induction period to achieve hemodynamic stability during intubation and to improve coronary blood flow.

Anesthetics administered were as follows: fentanyl 250µg followed by infusion, midazolam 1 mg, propofol infusion, rocuronium 50 mg followed by infusion and sevoflurane titrated between 1-3%. Patient was intubated with 7.5 size ETT under direct visualization of vocal cords. She was hooked to ventilator with the setting as follows: volume controlled ventilation, tidal volume 450 ml, RR 14 per minute, IE ratio 1:2 and FiO2 1.

during surgery. Proton pump inhibitor and dexamethasone 15 mg iv in a gauge 16 peripheral IV line were administered during preinduction period.

Transesophageal echocardiography (TEE) done after induction showed a dilated aortic root of 44 mm x 38 mm (normal < 37mm)[41] and proximal ascending aorta 35 mm x 27 mm (normal is 30 mm)[21] with dissection of the posterior aortic wall from the aortic root to the descending thoracic aorta of 32 mm (normal 18 – 22 mm)[21] with thrombus formation at the false lumen. There was also moderate to severe aortic regurgitation with mild mitral and tricuspid regurgitation.

Citicholine 1 gm, tranexamic acid 2 g were administered. Nitroglicerine drip, low dose dopamine drip and blood transfusion were started. Median sternotomy commence 29 hours from onset of symptoms or five hours from arrival at the emergency department. Heparin at 3 mg/kg was administered. Activated coagulation time (ACT) level of 375 was achieved before cannulation of the axillary artery, femoral artery and right atrium. ACT determination was done every 30 minutes to maintain a level above 350.

Surgery proceeded with a period of cardiac arrest by infusion of cardioplegic solution into the aortic root. Deep hypothermia at 20°C was achieved by infusion of cold blood using CPB, application of blanket roll and ice pack over the head. After the core temperature of 20C was achieved, innominate artery was clamped.

Blood cardioplegic solution was given in retrograde manner to facilitate the aortic root replacement with a composite valve graft. During this period of time, antegrade cerebral perfusion technique was used to provide blood flow to the brain. Perfusion to other organs was also preserved through femoral artery cannulation Rewarming of the temperature to 28°C was then initiated and maintained during completion of the coronary artery bypass of the right main coronary artery using a distal saphenous vein graft.

All anesthetic agents were given by continuous intravenous infusion. Total DHCA time, clamped/ischemic time and CPB time were 24 minutes, 155 minutes and 190 minutes respectively.

After rewarming to 37˚C, the bypass was gradually terminated. Heparin reversal with protamine was administered intravenously.

The post cardiopulmonary bypass course was uneventful. The PAP was maintained at 17-30/15-20 mmHg, ejection fraction was 69% compared to 63% preoperatively.

The modified Bentall surgery lasted 7 hours. Total blood loss was 1000 cc (maximal allowable blood loss was 252 cc) with total urine output of 1350 cc. Blood products transfused were PRBC of 4 units, FFP of 3 units and platelet concentrate of 5 units.

She was maintained on mechanical ventilator for six hours at the post anesthesia care unit (PACU). Postoperative fetal heart tones could not be appreciated. Pelvic ultrasound showed fetal demise. Expectant management for the intrauterine fetal demise (IUFD) was the best option at this time.

Patient was transferred to coronary care unit sedated but arousable with pain controlled by tramadol infusion and later by oral combination of paracetamol 325 mg and tramadol 37.5 mg.

On 2nd post op day, left ventricular dysfunction was noted on 2D echo with dyskinesia on the entire interventricular septum and hypokinesia on the anterior left ventricle (LV) free wall with best contraction at the antrolateral and inferolateral LV free wall (EF 33% by Tiechholz and 49% by Simpson's).

Dobutamine drip 5-15 mcg/kg/min was started and titrated. Fondaparinux 2.5 mg was also administered subcutaneously as an antithromboembolic agent. Other management includes general liquid diet progressive heart delight, humulin R sliding scale, calcium 600 mg, Vit D 400 IU tablet p.o. and potassium chloride tab 750 mg p.o. Neurologic examinations revealed same as preinduction.

Repeat 2D echo on 4th post op day showed an improvement in LV function (EF 51% by Simpson's) and wall motion (hypokinesia of entire septum).

She stayed at the coronary care unit for 6 days. No evidence of neurologic, nephrologic deficit, pulmonary and cardiac problems was noted. . Patient was discharged with improvement and preferred to be transferred to another hospital for delivery of the fetus.

***Discussion***

We are presented with a patient with aortic aneurysm with dissection type A. This requires immediate surgical intervention because of 50% risk of rupture.[2,24,32]

The presence of aortic dissection and systemic features with score ≥7 made our patient fulfill criteria of having Marfan syndrome following the 2010 Revised Ghent nosology criteria (see Appendix B). The aortic dissection in Marfan's syndrome patient usually manifests during pregnancy which happened in this case.

Type A dissection, meaning dissection involving the ascending aorta (Fig. 2) present in the patient, carries the risk of neurologic sequelae when the aorta is clamped.

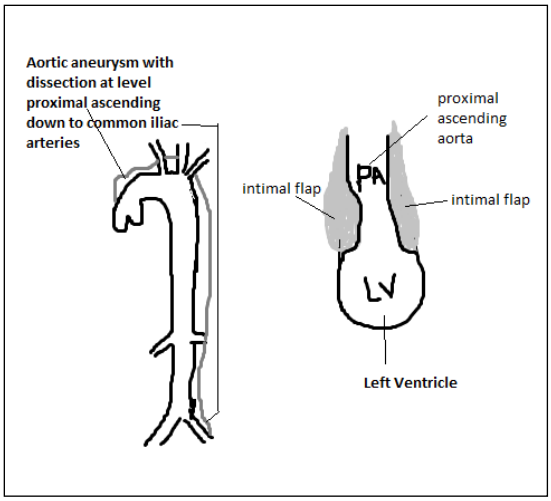


**Figure 2.** Type A aortic aneurysm and dissection at the level of the proximal ascending down to the common iliac arteries (left) and intimal flap from proximal ascending aorta (right)

In addition, the presence of more than 50 % stenosis of the left carotid artery, though not yet an indication for carotid endarterectomy, also added to the risk of cerebral ischemia. Thus, cardiopulmonary bypass and deep hypothermic circulatory arrest techniques, defined as the use of systemic hypothermia (core temperature of 14-20°C)[3] and the intentional cessation of the circulation for periods up to 60 minutes[30], were employed by placing the patient at 20°C to reduce the cerebral metabolic rate and oxygen consumption, and thus minimize the complication of cerebral ischemia.

Recurrence of aortic dissection in this patient is likely to happen especially during subsequent pregnancy.[19,23] Thus, grafting of the aortic dissection will not be enough. There should also be an aortic valve replacement and reimplantation of the left coronary ostium with a long interposed graft wrapping behind the grafting of the aortic dissection.[38]

The type A aortic dissection which also disrupted the right coronary artery blood flow (Fig. 3) required the patient to undergo coronary artery bypass graft in addition to the aortic dissection surgery and aortic valve replacement. Thus, the extension of the duration of the surgery is unavoidable.

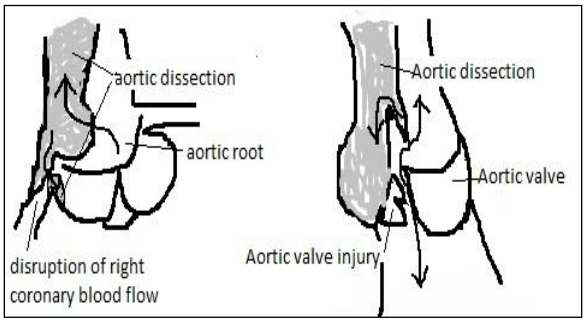


**Figure 3.** Disruption of the right coronary blood flow (left) and injury to the aortic valve due to aortic dissection causing moderate-severe aortic regurgitation (right)

However, the problems did not end there. The patient was also a primi gravid at 28 weeks AOG. Her prenatal check up and work-ups were not available. Referral to the Obstetric department could not find any indication for elective caesarian section at that time. The patient was not in labor. The fetal lung was expected to be immature as surfactant would be released at 30 weeks AOG, at which time could be detected in amniotic fluid.[42] Forty eight hours of steroids (dexamethasone every 12 hours for 4 doses or bethametasone every 24 hours for 2 doses) should be administered to accelerate fetal lung maturation.[11] However, the emergent nature of the surgical condition could not afford to wait 48 hours. Aspiration of amniotic fluid to detect the presence of surfactant at 28 weeks AOG seemed to have no beneficial effect.[42]

If elective caesarian section was done in a preterm patient who is not in labor and with very low birth weight fetus with immature lung, the chance of survival of the fetus would be less than 50%.[10] Bleeding could be expected from the uterus during the caesarean section in full term pregnancy with blood loss as much as 500 ml – 1000 ml in 75% of women having a caesarean section in the Philippines and more than 1000 ml in 4% of that population.[18] Furthermore, the life of the post partum patient would be greatly endangered if the patient would undergo aortic surgery wherein anticoagulants would be administered.

The patient's condition would have more than 45% risk of mortality if not immediately operated.[24] An increase of 1-2% mortality was expected for every hour delay of surgery from onset of symptoms.[24]

The risks and benefits were explained to the patient and the relatives. The family and the physicians agreed to do the aortic surgery to save the life of the pregnant patient without any neurologic sequelae with the hope that the fetus would be able to survive the insult caused by the medical and surgical conditions.

The worst possible scenarios were also explained to the relatives. The worst possibility was that the patient and the fetus might not be able to survive the surgery. Another possibility was the patient might survive the surgery but with neurologic sequelae or with kidney problem or with lower extremity paralysis secondary to the clamping of the aorta, carotid stenosis and prolonged surgery. Yet, the more expected possibility was the patient might survive but the fetus might not.

Since the patient was brought to the emergency department 24 hours from onset of symptoms, the patient was immediately operated five hours after admission or 29 hours after onset of symptoms.
TEE was done after induction of GEA to determine the final surgery. Ascending aortic replacement, total arch replacement with reattachment of brachiocephalic branches with modified Bentall procedure (the replacement the aortic root and reimplantation the left coronary artery) were chosen to minimize the risk of the recurrence of the later-onset aneurysms and dissection of the aorta which commonly encountered in Marfan syndrome.[23]

The modified Bentall technique, which was reported by Svensson in 1992, is an aortic root's replacement using a composite valve graft (bileaflet mechanical valve attached to a polyester tube graft) involving a left coronary ostium's reimplantation using Kochoucous's button modification by leaving button's of aortic wall surrounding both coronary arteries, which are then mobilized and sutured to the aortic graft (Fig 4).[38, 48]
Standard cardiopulmonary bypass (heart lung machine) and deep hypothermic circulatory arrest were achieved to facilitate the aortic dissection repair, valve replacement and CABG. Usual cannulation was impossible to use due to the location of the aortic dissection, thus axillary and femoral arteries were used for site of cannulation to maintain blood flow to the brain and other organs.

The patient was extubated six hours post surgery without any neurologic sequelae.

**Figure 4.** Illustration of the modified Bentall procedure for aortic root replacement, during which buttons of aortic wall surrounding coronary arteries are mobilized and sutured to the aortic graft. (Reprinted from Schwartz's Principles of surgery, 8th edition, 2004)

However, fetal heart tone could no longer be appreciated post operatively. Thus, though the difficult CABG and aortic surgery can be considered a success, the demise of the fetus intrautero made its success not in toto.

Aware of the all the consequences that might occur, the patient and the relatives appreciated the effort of the team who was able to prevent the worst possibilities that might occur to the patient.

The anesthetic management for modified bentall procedure in a pregnant patient with Acute Type A dissection is very challenging since there are two patients involved, mother and child. The additional risk for higher maternal morbidity which related to Marfan syndrome also made the nature of the event more challenging for any anesthesiologist.

Although the aim is life for both, survival of one without neurologic sequelae is already considered a success.

## Conclusion

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Review Article

# Prolaps Organ Panggul

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***Abstract***

Pelvic organ prolapse is a condition of descent or herniation of woman's pelvic organs through the birth canal or onto birth canal space. As someone gets older, the incidence of pelvic organ prolapse increases, due to weakening of ligaments and muscles as suspensor for the pelvic organs. Prolapse may or may not show symptoms. Symptoms that occur are associated due to pressure of the pelvic area, difficulty urinating and defecation. The staging of pelvic organ prolapse utilized the Baden-Walker System and Pelvic Organ Prolapse Quantification (POP-Q). Management for pelvic organ prolapse can be done conservatively and operatively, and the decision of which approach should be taken based on the patient's condition and choice.

**Key Word: Pelvic organ prolapse, Baden-Walker system, Pelvic Organ Prolapse Quantification (POP-Q)**

**Abstrak**

Prolaps organ panggul merupakan kondisi dimana terdapat penurunan atau penonjolan organ-organ yang berada pada rongga panggul wanita kedalam liang jalan lahir sampai keluar dari jalan lahir. Kejadian prolaps tersebut akan meningkat seiring bertambahnya usia seseorang yang disebabkan melemahnya struktur ligamen dan otot yang menjadi penyangga organ panggul tersebut. Prolaps yang terjadi dapat tidak menimbulkan gejala sampai terdapat gejala yang berhubungan dengan penekanan pada area panggul, sulit buang air kecil dan buang air besar. Dalam menilai stadium prolaps yang terjadi pada pasien dapat menggunakan sistem Baden-Walker dan Pelvic Organ Prolapse Quantification (POP-Q). Tatalaksana pasien dengan prolaps organ panggul dapat dilakukan secara konservatif dan tindak operatif, dimana tindakan yang akan dilakukan ditentukan dari kondisi pasien dan pilihan pasien.

**Kata Kunci: Prolaps organ panggul, Sistem Baden-Walker, Pelvic Organ Prolapse Quantification (POP-Q)**

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## Definisi

Prolaps Organ Panggul atau *Pelvic Organ Prolapse* (POP) adalah penurunan atau penonjolan organ-organ yang terdapat pada rongga panggul wanita (rahim, kandung kemih, dan rektum) kedalam liang jalan lahir dan pada sebagian kasus keluar dari jalan lahir.[1,2]

## Insidensi

Secara global, insidensi wanita yang menderita POP sulit diprediksi dengan pasti oleh karena masih terbatasnya pelaporan kasus kepada fasilitas maupun tenaga ahli medis, namun kasus POP bisa dikategorikan cukup sering khususnya pada wanita yang menginjak usia lanjut. POP diperkirakan terjadi pada hampir setengah perempuan dengan usia diatas 50 tahun, dan diperkirakan satu dari sepuluh perempuan akan menjalani penatalaksanaan operasi pada usia diatas 80 tahun.[1] Meskipun hampir setengah dari wanita diatas usia 50 tahun yang pernah melahirkan ditemukan memiliki POP melalui pemeriksaan fisik, namun hanya ditemukan 5-20% yang simtomatik.[3] Prevalensi POP meningkat sekitar 40% tiap penambahan satu dekade usia seorang wanita, dengan POP derajat berat lebih banyak ditemukan pada wanita dengan usia tua, yaitu, 28%-32,3% derajat 1, 35%-65,5% derajat 2, dan 2-6% derajat 3.[4] Pada saat ini terdapat sekitar 11-19% wanita di negara maju menjalani operasi POP dengan usia rata-rata

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wanita yang menjalani operasi POP adalah 60 tahun.[5]

Di negara maju seperti Amerika Serikat terdapat sebanyak 200.000 operasi POP dilakukan per tahun dengan jumlah kasus operasi ulang atas indikasi rekurensi mencapai 30%.[6]

**Etiopatogenesis**

Dalam keadaan normal, organ-organ dalam rongga panggul wanita (rahim, kandung kemih, dan rektum) tersangga oleh struktur-struktur ligamen dan otot-otot rongga panggul; apabila struktur-struktur tersebut melemah oleh karena sering mengalami regangan maksimal atau *overstretching*; POP dapat terjadi.[1,3] POP dapat disebabkan oleh satu atau lebih kombinasi faktor resiko. Salah satu faktor resiko POP adalah riwayat mengandung dan bersalin yang menjadi penyebab melemahnya struktur dasar panggul

Faktor resiko lain seperti genetik dan biokimia yang hingga saat ini masih diteliti juga dipercaya mempunyai peran penting dalam tendensi secara alamiah terjadinya POP.[3]

**Klasifikasi**

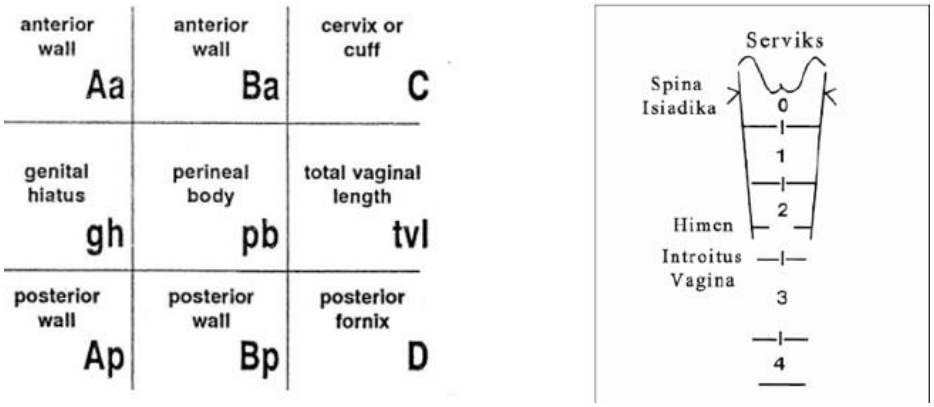
Secara keseluruhan terdapat empat tipe prolapse bergantung pada organ panggul yang menonjol ke jalan lahir (rahim, kandung kemih, rektum, vagina atau gabungan): (1) Prolaps dinding anterior (*Cystocele*) yang merupakan penonjolan kandung kemih ke dinding depan jalan lahir, (2) (otot levator ani, nervus pudendus, dan fasia penyokong organ panggul); faktor resiko ini dapat digolongkan lebih lanjut menjadi: (1) riwayat multigravida/paritas per vaginam, (2) riwayat mengandung bayi berukuran besar, (3) riwayat bersalin berkepanjangan atau, (4) riwayat melahirkan dengan bantuan forsep/*ventouse*. Selain itu melemahnya otot dasar panggul pada usia tua, khususnya setelah menopause oleh karena defisiensi estrogen juga menjadi salah satu faktor resiko. Berat badan yang tergolong *overweight* (Indeks Massa Tubuh/IMT tinggi) serta riwayat peningkatan tekanan intraabdomen oleh karena kebiasaan mengedan lama, mengangkat barang berat, batuk kronik, atau konstipasi kronik juga dapat meningkatkan keregangan otot dasar panggul sehingga dapat menyebabkan POP. Pada wanita yang telah menjalani histerektomi atas indikasi POP, prolaps puncak vagina (*vault prolapse*) lebih sering terjadi.

Prolaps dinding posterior (*Rectocele*) yang merupakan penonjolan rektum ke dinding belakang jalan lahir, (3) Prolaps uteri yang merupakan penonjolan rahim kedalam hingga keluar dari jalan lahir, dan (4) Prolaps puncak vagina (*Vault Prolapse*) yang merupakan penonjolan puncak vagina kedalam jalan lahir yang biasanya terjadi pasca operasi histrektomi.[2]

Untuk keperluan praktik klinis, sistem *Baden-Walker* (Gambar 1) telah digunakan secara luas, sementara sistem *Pelvic Organ Prolapse Quantification (POP-Q)* (Tabel 1) mulai banyak digunakan untuk keperluan praktik klinik dan penelitian.[3]

Tabel 1. Klasifikasi Sistem POP-Q dan Sistem Baden-Walker

| **Sistem POP-Q** | **Sistem Baden-Walker** |
|---|---|
| Sangat detil untuk keperluan praktik klinik | Adekuat untuk keperluan praktik klinik, asalkan seluruh kompartemen dinilai |
| Adekuat untuk kepentingan penelitian | Mengukur penurunan relatif terhadap himen |
| Sangat baik untuk menilai perubahan derajat POP | |
| Derajat didasarkan pada penurunan maksimal dari prolaps relatif terhadap himen, pada 1 atau lebih kompartemen | |
| Stadium prolaps uteri dibagi menjadi 5 stadium, yaitu:<br>• Stadium 0: tidak tampak prolaps uteri. Titik Aa, Ap, Ba, dan Bp semuanya -3 cm dan titik C atau D terletak di antara –TVL (total vaginal length) dan –(TVL-2)cm.<br>• Stadium I: kriteria untuk stadium 0 tidak ditemukan, tapi bagian distal prolaps > 1cm di atas level hymen.<br>• Stadium II: bagian paling distal prolaps uteri ≤ 1 cm proksimal atau distal hymen.<br>• Stadium III: bagian paling distal prolaps uteri > 1 cm di bawah hymen tetapi tidak menurun lebih dari 2 cm dari TVL.<br>• Stadium IV: eversi komplit total panjang traktur genitalia bawah. Bagian distal prolaps uteri menurun sampai (TVL-2)cm. | *Stadium prolaps uteri dibagi menjadi 5 bagian berdasarkan turunnya bagian terbawah organ*<br>• Stadium 0: Posisi normal untuk tiap lokasi<br>• Stadium 1 : Penurunan sampai dengan setengah jarak *(halfway)* menuju himen<br>• Stadium 2: Turun sampai dengan himen<br>• Stadium 3: Turun setengah jarak *(halfway)* melewati himen<br>• Stadium 4: Penurunan maksimum untuk tiap lokasi |




Gambar 1: Klasifikasi Sistem Baden-Walker

**Diagnosis**

Diagnosis POP dapat ditegakan berdasarkan anamnesis, pemeriksaan fisk dan pemeriksaan penunjang. Berdasarkan anamnesis dapat diperoleh gejala berdasarkan compartment organ yang mengalami prolapse, gejala-gejala tersebut dapat berupa (Tabel 2):[3,8,9]

Tabel 2: Gejala dan Tanda Klinis POP

| Gejala sesuai kompartemen | Gejala |
|---|---|
| Gejala Vagina (semua kompartemen) | Terasa benjolan |
| | Rasa tertarik di perineum |
| | Tekanan pada panggul |
| | Rasa tidak nyaman |
| | Duh tubuh atau keluar darah dari ulkus dekubitus |
| Gejala Berkemih (kompartemen anterior) | Sulit memulai berkemih |
| | Berkemih tidak lampias |
| | Inkontinensia urin |
| | Urgensi |
| | ISK berulang |
| Gejala BAB (kompartemen posterior) | Benjolan pada liang vagina saat mengedan |
| | BAB tidak lampias |
| | Inkontinensia alvi |
| | Perlunya penekanan pada perineum atau vagina posterior untuk membantu BAB |
| Gejala seksual (semua kompartemen | Menurunnya sensasi vagina |
| | Dispareunia |
| | Menghindari hubungan seksual |

Intensitas Gejala dipengaruhi oleh dua faktor lain mencakup: (1) gravitasi sehingga makin berat pada posisi berdiri. (2) aktifitas fisik sehingga benjolan akan terasa semakin menonjol terutama setelah mengangkat benda berat atau berdiri. Derajat prolaps tidak berhubungan dengan gejala urgensi, frekuensi atau inkontinensia urin. Korelasi antara gejala BAB dan prolaps posterior lebih kuat dibandingkan korelasi antara gejala berkemih dengan prolaps anterior. Gejala tambahan seperti rasa tekanan, ketidaknyamanan, benjolan yang terlihat dan gangguan seksual tidak spesifik pada kompartemen tertentu. Kuesioner yang telah divalidasi yaitu *Pelvic Floor Distress Inventory (PFDI)* dan *Pelvic Floor Impact Questionnaires (PFIQ).*[3]

Pada pemeriksaan fisik biasanya dilakukan pemeriksaan ginekologi umum untuk menilai kondisi patologis lain seperti:[3,10,11](1) Inspeksi vulva dan vagina untuk menilai erosi atau ulserasi pada epitel vagina, ulkus yang dicurigai sebagai kanker harus dibiopsi segera, ulkus yang bukan kanker diobservasi dan di biopsi bila tidak ada reaksi pada terapi; (2) Pemeriksaan ada tidaknya prolaps uteri penting untuk mengetahui derajat prolaps uteri diawali dengan inspeksi terlebih dahulu sebelum dilakukan inspekulum; (3) Manuver valsava dapat menilai derajat maksimum penurunan organ panggul dilihat dengan melakukan pemeriksaan fisik sambil meminta pasien melakukan mengedan atau batuk. (4) Setiap kompartemen termasuk uretra proksimal, dinding anterior vagina, serviks, apeks, cul-de-sac, dinding posterior vagina, dan perineum perlu dievaluasi secara sistematis dan terpisah.[3]

Pemeriksaan penunjang yang dapat dilakukan dapat berupa pemeriksaan residu urin pasca berkemih, skrining infeksi saluran kemih, pemeriksaan urodinamik, dan pemeriksaan ultrasonografi pelvis yang relatif mudah dikerjakan, *cost-effective*, banyak tersedia dan memberikan informasi *real-time*.[3,12,13,14]

**Tatalaksana**

Penanganan POP dapat berupa penanganan konservatif/non-bedah dan penanganan operatif/bedah. Penanganan konservatif perlu didiskusikan dengan semua wanita dengan prolapse diawali dengan penanganan konservatif non-spesifik yang mencakup rehabilitasi otot dasar panggul dan *symptom directed theraphy* pada prolaps derajat I atau II dengan gejala non-spesifik berupa: (1) Penurunan berat badan dan olah raga, (2) Terapi perilaku dengan BAB dan BAK terjadwal, (3) Modifikasi diet dengan makanan berserat dan pemberian supplemen, (4) Pembatasan cairan, (5) Penggunaan laksatif atau enema dan obat-obat simptomatis lain sesuai indikasi. Pada prolaps grade lanjut dapat dilakukan lanjutkan dengan penanganan konservatif spesifik dengan pemasangan instrumen pesarium dengan bentuk bervariasi sesuai dengan indikasinya. (Figure 3) [3,15,16,18]

Penaganan operatif/bedah telah diteliti memiliki dampak jangka panjang yang lebih baik dalam meningkatkan kualitas hidup wanita. Prosedur penanganan operatif bervariasi sesuai kompartmen atau organ-organ yang mengalami prolapse (Tabel 3).[3,17,18]

Tabel 3: Jenis Pesarium dan Indikasinya

| Tipe | Mekanisme Kerja | Indikasi | Keterangan |
|---|---|---|---|
| Ring | Suportif | Sistokel, penurunan uterus ringan | Ketebalan, ukuran, dan rigiditas bervariasi |
| Donut | Suportif | Semua prolaps kecuali defek posterior berat | |
| Lever | Suportif | Sistokel, penurunan uterus ringan | Mengikuti kurvatura vagina |
| Dish | Suportif | Prosidensia berat | |
| Stem | Suportif | Sistokel, Prosidensia ringan | |
| Cube | Mengisi ruang | Semua prolaps | Perlu dilepaskan setiap hari |
| Inflatable | Mengisi Ruang | Semua Prolaps | Perlu dilepaskan setiap hari |

Pada kasus prolaps uteri dapat dilakukan histrektomi total, pada kasus prolapse puncak vagina pasca histrektomi dapat berupa colpopexy sacral abdominal dan suspensi transvaginal untuk fiksasi ligamen sacrospinous, ligamen uterosacral dan otot atau fasia iliokoksigeus. Pada wanita yang memiliko risiko komplikasi operasi atau anestesi yang dikontraindikasikan untuk operasi, maka penatalaksanaan nonbedah menjadi pilihan utama dan kolpokleisis (kolpektomi) dapat ditawarkan. Pada wanita yang memilih penatalaksanaan bedah namun menginginkan preservasi uterus dapat dilakukan prosedur fiksasi ligament sakrospinosus atau uterosakral, atau dilakukan histeropexy per abdominal tanpa dilakukan histerektomi.[3,18]

Pada kasus prolapse anterior (sistokel) dapat ditatalaksana dengan kolporafi anterior tradisonal dengan atau tanpa menambahan jaring sintetik (*mesh*) atau materi tandur (*graft*).[3,18]

Prolaps posterior (rektokel) ditatalaksana dengan menggunakan kolporafi posterior, dengan plikasi garis tengah (mid-line) jaringan vagina subepitel.[3,1]

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## PETUNJUK PENULISAN NASKAH

Medicinus, Jurnal Kedokteran Universitas Pelita Harapan, adalah publikasi bulanan yang menggunakan sistem *peer review* untuk seleksi artikel. Medicinus menerima artikel penelitian asli yang relevan dengan bidang kesehatan dan kedokteran, baik yang merupakan ilmu-ilmu dasar maupun terapan/klinik. Medicinus juga memuat tinjauan pustaka, laporan kasus, penyegar ilmu kedokteran, tinjauan buku baru, dan ceramah.

- **Artikel Penelitian**
  Berisi artikel tentang hasil penelitian asli dalam ilmu kedokteran dasar atau terapan.
  Format terdiri dari **pendahuluan, bahan dan cara kerja/metode, hasil, dan pembahasan**.

- **Tinjauan Pustaka**
  Artikel ini merupakan kaji ulang mengenai masalah-masalah ilmu kedokteran dan kesehatan yang mutakhir.
  Format terdiri dari **pendahuluan, isi, ringkasan, dan kesimpulan**.

- **Laporan Kasus**
  Suatu artikel yang berisi tentang kasus-kasus klinik menarik sehingga baik untuk disebarluaskan kepada rekan-rekan sejawat.
  Format terdiri dari **pendahuluan, laporan kasus, dan pembahasan**

- **Penyegar Ilmu Kedokteran**
  Artikel ini memuat hal-hal lama tetapi masih up to date.
  Format **sama dengan tinjauan pustaka**.

- **Ceramah**
  Merupakan suatu tulisan dan laporan di bidang dunia kedokteran/kesehatan yang harus disebarluaskan.
  Format **sesuai dengan naskah asli ceramah**.

- **Tinjauan buku baru**
  Suatu tulisan mengenai buku baru di bidang kedokteran/kesehatan yang akan menjadi sumber informasi bagi pembaca.
  Format terdiri dari **pendahuluan, isi buku dan kesimpulan**.

### PETUNJUK UMUM

Naskah yang dikirim belum pernah dipublikasikan dalam majalah ilmiah manapun. Penulis utama harus telah memastikan bahwa seluruh penulis pembantu telah membaca dan menyetujui naskah yang dikirim.

Naskah ditulis dalam bahasa Indonesia atau Inggris. Isi artikel tidak menjadi tanggung jawab redaksi. Semua naskah yang dikirimkan ke Medicinus akan dibahas oleh para pakar bidang keilmuan yang bersangkutan (***peer-review***) dan redaksi. Naskah yang memerlukan perbaikan akan dikembalikan kepada penulis untuk diperbaiki. Semua artikel penelitian yang diterbitkan harus telah mendapatkan **persetujuan komite etik** dan melampirkan ***informed concent*** bila penelitian berkaitan dengan subyek manusia.

### PENULISAN ARTIKEL

Naskah lengkap diketik pada kertas berukuran 21x30 cm (kertas A4) dengan dua spasi, jumlah halaman 10-15 lembar. Naskah yang dikirim ke redaksi adalah asli disertai dengan 2 kopi naskah termasuk foto, disket, atau CD. Tuliskan nama file dan program yang digunakan pada label disket atau CD. Artikel dan foto/disket/CD yang dikirim untuk Medicinus harus disertai dengan surat pengantar dan *checklist* yang telah diisi dan ditandatangani oleh seluruh penulis.

### HALAMAN JUDUL

Halaman judul harus berisi judul artikel (tidak ada penyingkatan kata), nama lengkap dengan gelar akademik tertinggi, lembaga/institusi penulis, nama dan alamat penulis utama, sumber pendanaan bila dalam bentuk hibah. Judul singkat dengan jumlah maksimal 40 karakter termasuk huruf dan spasi.

### ABSTRAK DAN KATA KUNCI

Abstrak untuk artikel penelitian, tinjauan pustaka dan laporan kasus dibuat dalam bahasa Indonesia dan Inggris dengan jumlah 150 – 250 kata. Abstrak hendaknya dibuat ringkas dan jelas sehingga pembaca memahami aspek penting tanpa harus membaca seluruh naskah.
Pilih 3 – 10 kata atau frase pendek yang dapat membantu penyusunan indeks artikel.

### TEKS ARTIKEL

Teks artikel harus disusun menurut subjudul yang sesuai, yakni Pendahuluan, Metode, Hasil, dan Diskusi.
Ukuran satuan menggunakan *System International Units* (SI Units), dan jangan menggunakan singkatan yang tidak baku. Singkatan untuk ukuran dibuat sesuai dengan *Style Manual for Biological Sciences*, seperti mm, kcal dll.

### TABEL DAN GAMBAR

Setiap tabel harus diberi judul, nomor dengan angka Arab dan diketik 2 spasi. Penjelasan tabel diletakan pada catatan kaki. Jumlah tabel maksimal 6 buah.
Setiap gambar atau foto harus memiliki identitas nama penulis, nomor, tanda petunjuk bagian “atas” gambar. Tandai juga bagian “depan”. Bila gambar/illustrasi pernah di publikasi maka harus disertai izin tertulis. Jumlah gambar maksimal 6 buah.

### METODE STATISTIKA

Metode statistika yang digunakan diterangkan secara detail pada bagian “Metode” dan metode yang tidak lazim harus didukung dengan rujukannya.

### UCAPAN TERIMAKASIH

Ucapan terimakasih dibatasi pada para professional yang membantu penyusunan naskah, termasuk pemberi dukungan dana/teknis/dukungan dari institusi.

### RUJUKAN

Cara penulisan rujukan mengikuti **kaidah Vancouver** dengan nomor urut sesuai dengan pemunculan dalan keseluruhan teks artikel, bukan menurut abjad. Penggunaan abstrak sebagai rujukan hendaknya dihindari. Apabila akan menggunakan naskah yang telah dikirim tetapi belum diterbitkan sebagai rujukan hendaknya disebut dengan pengamatan yang belum dipublikasikan (*unpublished observations*) dan seizin dengan sumber. Bila menggunakan naskah yang telah diterima tetapi belum terbit pakailah perkataan “*in press*”. Rujukan berupa komunikasi pribadi sebaiknya dihindari.
Contoh menuliskan rujukan :

**Buku dan monograf lain**

Catatan:

- Bila terdapat enam atau kurang dari enam penulis, anda harus menulis nama semua penulis.
- Bila terdapat tujuh atau lebih penulis, hanya enam penulis pertama yang ditulis dan tambahkan dengan "et al"
- Pada penulisan nama penulis menurut **kaidah Vancouver** harus mengunakan koma dan memberikan satu ruang diantara setiap nama. Setelah nama penulis terakhir pakailah tanda titik penutup.

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