**EDITORIAL**

# Daily Application of Evidence-Based Medicine

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David Sackett, widely recognised as "the father of evidence-based medicine (EBM)", has defined EBM as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients [which involves] integrating individual clinical expertise with the best available external clinical evidence from systematic research".[1] In its initial introduction, EBM has been criticized as being restrictive to the practice of medicine, so far as to calling it 'recipe medicine'.[2] However, it is clear from its definition that in its philosophy, EBM is based on the best available evidence and clinician expertise, in consideration of the patients' needs and preferences.

It has become clear that to be able to practice EBM in their daily practice, clinicians need high-quality, reliable, and easily accessible evidence sources. This availaibility and accessibility of good evidence has been noted as one of the barriers of EBM in daily practice.[3,4]

Further augmenting the problem is the fact that the evidence base is never static and constantly shifting. What is once considered best practice and safe, may be scrutinized and considered unsafe as further evidence emerges. This brings about the dilemma of keeping up with the evidence. How will clinicians, especially obstetricians and gynecologists, follow the relentless development of evidence while managing their daily practice? The presence of 'evidence summaries' such as Cochrane systematic reviews and BMJ 'Best Practice', as well as periodic 'alert systems' offer assistance to clinicians in staying up-to-date with important updates from their respective fields.[5]

A further problem recognized in EBM is how to determine what is 'best' evidence. Literature can be misleading, and since evidence 'never speaks for itself' it is never free from bias.[6,7] Several ways can be employed to avoid being misled by what is written in the literature. Firstly, we should always apply caution when assessing the discussion section as this is where authors typically 'spin' their findings. Second, we should be aware of surrogate outcome measures that are not of clinical importance, composite outcome measures, and inappropriate comparators, especially in randomized clinical trials. Thirdly, great care should be taken when reading papers demonstrating 'non-inferiority' or 'equivalence', as this is most commonly interpreted by readers. Finally, trials that are stopped early must always be considered with suspicion, since this may lead to a falsely large effect size in similar subsequent trials.[5,8]

Despite the wide acceptance of EBM in modern day medicine, limitations in the practice of EBM still exist. Increased connectivity and availability of evidence is valuable in developing the practice of EBM but clinicians should apply constant vigilance and take into account clinical experience and patients' condition before applying evidence into daily practice.

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Research Article

# Husband's Support is a Main Factor Associated with Contraceptive Practices

## *Dukungan Suami adalah Faktor Utama yang Berhubungan dengan Perilaku Penggunaan Kontrasepsi*

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## Abstract

**Objective:** To determine factors associated with contraceptive practices in Palabuhanratu, West Java.

**Method:** We conducted a cross-sectional study at the Obstetrics and Gynecologic ward of Local General Hospital of Palabuhanratu District, between March and June 2012. Data was collected using directed interview method by investigators and midwives, using non-validated questionnaires. Statistical analysis was performed using SPSS 20.0, utilizing Chi-Square test for nominal data and Kruskal-Wallis test for numerical data.

**Result:** We obtained 71 samples. The only factors which are significant were age group of 20-35 years old (OR=3.5, 95%CI=1.1-11.1, p=0.025) and husband's support (OR=14.67, 95%CI=1.52-141.18, p=0.012). The most recognized contraceptive methods familiar to our respondents were injection (94.4%) and pills (93.0%), and the most useful source of information on contraception was medical personnel (73.2%).

**Conclusion:** Husband's support is a main factor associated with contraceptive practice. The choice of contraceptive method should be adjusted according to the ability and desire of patients to prevent failures in family planning.

[Indones J Obstet Gynecol 2015; 3: 123-126]

**Keywords:** associated factors, contraception, husband's support

## *Abstrak*

***Tujuan:*** *Menentukan faktor yang berhubungan dengan penggunaan kontrasepsi di Palabuhanratu, Jawa Barat.*

***Metode:*** *Studi ini menggunakan rancangan potong lintang, dan dilakukan di Ruang Perawatan Obstetri dan Ginekologi, RSUD Palabuhanratu, Jawa Barat, mulai Maret 2012 hingga Juni 2012. Data diperoleh melalui wawancara terpimpin oleh peneliti dan bidan menggunakan kuesioner yang tidak tervalidasi. Analisis statistik dilakukan dengan program SPSS 20.0, menggunakan uji Chi-square untuk data nominal dan uji Kruskal-Wallis untuk data numerik.*

***Hasil:*** *Diperoleh 71 sampel. Faktor yang secara signifikan berhubungan dengan penggunaan kontrasepsi adalah kelompok umur 20-35 tahun (OR=3,5, IK95%=1,1-11,1, p=0,025) dan dukungan suami (OR=14,67, IK95%=1,52-141,18, p=0,012). Metode kontrasepsi yang paling banyak diketahui responden adalah suntik (94,4%) dan pil (93,0%). Sumber informasi mengenai kontrasepsi yang dirasakan paling bermanfaat adalah tenaga medis (73,2%).*

***Kesimpulan:*** *Dukungan suami adalah faktor utama yang berhubungan dengan penggunaan kontrasepsi. Pilihan metode kontrasepsi harus disesuaikan dengan kemampuan dan keinginan pasien.*

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***Kata kunci:*** *dukungan suami, faktor yang berhubungan, kontrasepsi*

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## INTRODUCTION

Indonesia is the fourth most populated country in the world. In 2011, Indonesia has a population amounting to around 240 million individuals with a population growth of 1.49% per year.[1] The relatively high population growth may impede target achievement of the Millennium Development Goals (MDG) 2015 in Indonesia.

Contraception has been considered as the main key to accomplish MDGs targets.[2] The Indonesian MDG progress report has generally suggested that there is increasing use of modern contraceptive methods. However, there are some areas regarded as the untouchables, which have no access to Family Planning and in those areas, the use of modern contraceptive remains low. This issue is consistent with the number of reproductive age couples who want to pace or limit pregnancies but do not use any contraceptive methods (unmet needs). The National MDG report in 2011 indicated that there was 9.7% of unmet needs and the rate has remained the same since 1997.[3]

Some efforts should be taken to reduce the unmet needs by identifying difficulties in providing contraceptive service, which indeed are different for

each region or population. In this study, factors correlated with positive attitude toward the use of contraceptive methods were investigated in Palabuhanratu district in West Java.

## METHODS

This study used a cross-sectional design and was conducted at the Obstetrics and Gynecology ward of Local General Hospital of Palabuhanratu District, West Java, between March-April and June 2012. The inclusion criteria were married reproductive age women, who were willing to be the respondents, while the exclusion criteria were women with infertility, parity ≤ 1, or marital status of widow/divorced. The obtained sample size was 71 subjects. Data was collected by directed interview method by investigators and midwives, using non-validated questionnaires. Data was processed using SPSS version 20.0. Data analysis was performed using Chi-Square test for nominal data and Kruskal-Wallis test for numeric data.

Our definition for positive attitude toward contraceptive method was a woman who ceased to use contraceptive method because she was planning for pregnancy with birth spacing between her current and previous pregnancy of at least 2 years, or a woman who was pregnant due to failure of contraceptive method, or a woman who was using contraception. Meanwhile, the negative attitude included women who did not use contraception or refused to use contraception.

## RESULTS

Out of 71 samples, we found 54 samples (76.1%) with positive attitude and 17 samples (23.9%) with negative attitude. Baseline data of all respondents is presented in Table 1.

**Table 1.** Baseline Data of All Respondents

| Parameter | Frequency (%) |
|---|---|
| Age (years) | |
| < 20 | 0 (0) |
| 20-25 | 2 (2.8) |
| 26-30 | 26 (36.6) |
| 31-35 | 21 (29.6) |
| >35 | 22 (31.0) |
| Educational status | |
| ≤ 9 years | 56 (78.9) |
| >9 years | 15 (21.1) |
| Income | |
| IDR <1 million | 55 (77.5) |
| IDR ≥ 1 million | 16 (22.5) |
| Number of marriage | |
| 1 | 58 (81.7) |
| >1 | 13 (18.3) |
| Parity | |
| 2 | 33 (46.5) |
| 3-5 | 33 (46.5) |
| >5 | 5 (7.0) |

**IDR = Indonesian Rupiah*

**Table 2.** Results of Comparative Analysis Between Investigated Factors and Attitude Towards Contraception

| Factors | Odds ratio (95%CI) | *p-value* |
|---|---|---|
| Age 20-35 years | **3.5 (1.1-11.1)** | **0.025** |
| Mother's education >9 yr | 0.55 (0.16-1.90) | 0.331 |
| Husband's education >9 yr | 0.58 (0.18-1.88) | 0.365 |
| Income ≥ 1 million/month | 1.48 (0.37-5.97) | 0.745 |
| Number of marriage | - | 0.416 |
| Parity | - | 0.798 |
| Desire of having ≤ 2 children | 0.35 (0.11-1.08) | 0.062 |
| Perception on obligatory family planning | 5.57 (0.85-36.66) | 0.085 |
| Working mother | 0.94 (0.17-5.14) | 1.000 |
| Husband's support | **14.67 (1.52-141.18)** | **0.012** |
| Family's support | 6.47 (0.55-75.84) | 0.239 |
| Support from traditioinal and local environment | 3.47 (0.45-26.73) | 0.241 |
| Support from health care personnel | 5.23 (1.039-26.33) | 0.052 |

A comparative analysis was performed comparing the investigated factors and respondents' attitude towards contraception. Analysis results and the significance are shown in Table 2.

The results indicate that factors which had significant correlation with the use of contraception were age of 20-35 years old (OR=3.5, 95%CI=1.1-11.1) and husband's support (OR=14.67, 95%CI=1.52-141.18). Other factors which also showed significant trend were support from health care personnel (p=0.052) and desire of having ≤ 2 children (p=0.062).

The most recognized contraceptive methods by our respondents were injection (94.4%) and pill (93.0%), and the most useful source of information on contraception was medical personnel (73.2%). The detailed recognized contraceptive methods and the most useful source of information are shown in Table 3 and 4.

**Table 3.** Contraceptive Method Known by Respondents

| Contraceptive Methods | Percentage (%) |
|---|---|
| Injectables | 94.4% |
| Pill | 93% |
| Intrauterine device | 54.9% |
| Implants | 52.1% |
| Sterilization | 39.4% |
| Condom | 29.6% |
| Lactational amenorrhea | 2.8% |
| Calendar system | 1.4% |
| Emergency contraception | 1.4% |

**Table 4.** The Most Useful Source of Information on Contraception

| Source of information | Percentage (%) |
|---|---|
| Medical personnel | 73.2% |
| Friend / neighbour | 46.5% |
| Family | 45.1% |
| Electronic media | 28.2% |
| Printed media | 9.9% |
| School | 2.8% |

In the group of positive attitude toward contraception, we found that 37% respondents experienced failure of family planning. The most common contraceptive method in the group with failed family planning was pills (60%), followed by injection (30%).

## DISCUSSION

Among the analyzed factors on their correlation with positive attitude toward applied contraception, age group of 20-35 years and husband's support were the only factors found to be significant. First, it should be noted that our study was a cross-sectional study; therefore, the calculation of odds ratio could only provide the correlation of association, instead of causality.

The age group in our study was categorized into the group of women delaying pregnancy (<20 years), the group of women spacing pregnancy (20-35 years), and the group of women who does not desire any pregnancy in the future (>35 years). In statistical analysis, the first and the third group were combined as a variable. A significant value found in the age group of 20-35 years (OR=3.5, 95%CI=1.1-11.1) showed that there was awareness in the group of spacing pregnancy. Moreover, subjects in the age group of <20 years were more likely to not use any contraceptive method due to their desires of having a first child. However, it should be noted that our study was conducted at the Obstetrics and Gynecology ward, which may cause selection bias since it did not include women who were using contraception and who were not pregnant.

Husband's support was the only modifiable factor found to be significant, in which it will increase the possibility of contraceptive method used by 14.67 folds (95%CI=1.52-141.18). Various studies have reported that husband's support was correlated to the use of contraception.[4,5] It has been proven that if the husband has the final decision on contraception in a household, the couple tends not to use contraception.[6] Therefore, communication between husband and wife is also an important factor in family planning.[7] Unfortunately, approximately only 60.3% of husbands discuss about family planning with their wife. Furthermore, in 33.3% of cases, husbands are the sole and final decision makers.[8] Information and counseling on contraception and family planning should be provided for the couple, husband and wife, and not only for single participants.[9]

Support from medical personnel, although was not significant in our study, is one of the important components increasing the coverage of contraception.[5] It is confirmed by our findings that information about contraception had been perceived as the most valuable when it came from medical personnel.

In our study, the education levels of husband and wife were not significantly correlated to positive attitude towards the use of contraception. It indicates that providing special information about contraception and family planning is more essential as the information is rarely discussed in formal educational activity.

Family support and the support from traditional and local environment had no significant contribution on positive attitude towards the use of contraception. It demonstrates that the support of both factors tend to have equal distribution in both behavioral groups. In other words, there were no family or local traditional habits that become obstacles against the use of contraception in Palabuhanratu district. This finding is different from results in a Cambodian study, which demonstrated that family prohibition would reduce the use of contraception by 50%.[4]

The most recognized contraceptive method by our respondents was injection (94.4%), which was followed by pills (93%), and IUD (54.9%). We can conclude that the most favorable contraceptive method was hormonal contraception. Our interview results revealed that many respondents were afraid to use IUD due to various reasons, such as their fear of IUD insertion pain and their reluctance of having a foreign body inside their womb. Similar findings have been reported in India, where many women refused to use IUD and preferred to listen to inputs from their friends and family than the information from health care personnel.[10] In women with high parity or age >35 years, specific education on long-term contraceptive methods should be provided. Considering that most respondents prefer hormonal contraceptive method, the intervention should be emphasized on implant as a contraceptive method.

In the group of subjects with positive family planning attitude, there was 37% of respondents who had experienced contraceptive failure. The most ineffective contraceptive method was pills (60%), followed by injection (30%). The high rate of contraceptive failure may be caused by bad choice when selecting contraceptive methods or errors when using the contraception. Therefore, counseling on the available contraceptive method is very important and it may help patients to select the best method for them according to their needs, know-ledge and ability. The choice of contraceptive me-thod should be adjusted to the ability and desire of patients to prevent failures in family planning.

## CONCLUSION

Husband's support is a main factor associated with contraceptive practice. The choice of contraceptive method should be adjusted with the ability and desire of patients to prevent failures in family planning.

## ACKNOWLEDGEMENTS

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Research Article

# Female Sexual Function at Three Months Post-delivery in Spontaneous Labor and Cesarean Section

## *Fungsi Seksual Perempuan pada Tiga Bulan Pascapersalinan Spontan dan Seksio Sesarea*

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## Abstract

**Objective:** To study the comparison of encouragement, stimuli, orgasm, pain and satisfaction of female sexual function at 3 months postpartum between spontaneous delivery and cesarean section in Dr. Cipto Mangunkusumo Hospital in Jakarta.

**Method:** This was an observational research, sexual function was measured at three months post-delivery with Female Sexual Function Index (FSFI) questionnaire. The study design used was cross sectional with consecutive sampling. Analysis for comparative nonpaired categorical variables was done using Chi square or Fisher analysis. Analysis for confounding variables was carried out using multivariate logistic regression.

**Result:** From 150 respondents, 43.3% had sexual dysfunction, with 52% of the spontaneous labor group and 34% of the cesarean section group. Bivariate analysis showed that occurrence of sexual dysfunction at three months post-spontaneous labor was 1.5 times higher (95% CI 1.02-3.19) compared with cesarean section. Sexual encouragement shows a two-fold difference (95% CI 1.17-3.40) compared to cesarean section. However, orgasm disturbance was 8 times higher (95% CI 1.90-3.58) in the spontaneous labor group, with confounding variable of perineal rupture. Disturbance of sexual stimuli, satisfaction, and pain were not significantly different between spontaneous labor and cesarean section. Multivariate analysis found that spontaneous labor was statistically significant for sexual dysfunction at three months post-delivery in patients with sexual encouragement (RR=2.716, p=0.008) and orgasm accession dysfunction (RR= 6.952, p=0.031). However, the more than 30 years old of age variable was statistically significant in sexual dysfunction variable with RR= 2.60 and p=0.021.

**Conclusion:** Spontaneous labor is statistically significant for sexual dysfunction at three months post-delivery, especially for sexual encouragement and orgasm accession. Meanwhile, the variables with the age of 30 years old or older of age were influential on sexual dysfunction, especially to the sexual stimuli variable.

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**Keywords:** labor method, sexual dysfunction, three months post-delivery

## *Abstrak*

***Tujuan:*** *Mengetahui perbandingan dorongan, bangkitan, orgasme, nyeri dan kepuasan seksual perempuan 3 bulan pascapersalinan pada persalinan spontan dan seksio sesarea di Rumah Sakit Dr. Cipto Mangunkusumo, Jakarta.*

***Metode:*** *Penelitian ini adalah penelitian observasional, dengan subjek kelompok persalinan spontan dan seksio sesarea, yang dilakukan pengukuran fungsi seksualnya 3 bulan pascapersalinan menggunakan kuesioner Female Sexual Function Index (FSFI), dengan desain penelitian potong lintang dan pengambilan sampel consecutive sampling. Analisis komparatif katagorik tidak berpasangan menggunakan Chi square atau uji Fisher. Analisis variabel perancu dilakukan dengan analisis multivariat regresi logistik.*

***Hasil:*** *Dari 150 responden pascapersalinan spontan dan seksio sesarea didapatkan 43,3% mengalami disfungsi seksual dengan 52% kelompok persalinan spontan dan 34% kelompok seksio sesarea. Analisa bivariat menunjukkan terjadinya disfungsi seksual 3 bulan pascapersalinan spontan 1,5 kali lebih besar (IK 95% 1,02-3,19) dibandingkan seksio sesarea. Gangguan hasrat/dorongan seksual 2 kali lebih besar (IK 95% 1,17-3,40) dibandingkan seksio sesarea, sedangkan gangguan orgasme 8 kali lebih besar (IK 95% 1,90-3,58) dengan variabel perancu yaitu robekan perineum. Gangguan bangkitan seksual, lubrikasi, kepuasan seksual dan nyeri tidak berbeda secara bermakna antara persalinan spontan dan seksio sesarea. Analisa multivariat variabel persalinan spontan bermakna secara statistik untuk disfungsi seksual pasien 3 bulan pascapersalinan pada variabel disfungsi dorongan seksual (RR=2,716, p=0,008) dan pencapaian orgasme (RR= 6,952, p=0,031), sedangkan variabel usia lebih dari 30 tahun bermakna secara statistik pada disfungsi seksual pada variabel bangkitan seksual dengan p=0,021 dan RR=2,601.*

***Kesimpulan:*** *Persalinan spontan bermakna secara statistik untuk terjadinya disfungsi seksual 3 bulan pascapersalinan, terutama untuk variabel dorongan seksual dan tercapainya orgasme. Sedangkan variabel usia lebih dari 30 tahun merupakan variabel yang berpengaruh pada disfungsi seksual, terutama pada variabel bangkitan seksual.*

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***Kata kunci:*** *disfungsi seksual, metode persalinan, tiga bulan pascapersalinan*

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## INTRODUCTION

Changes in women's sexual function after childbirth ranges from 23%-86% and has a significant impact on family harmony. Various studies on female sexual function after childbirth have performed the comparison of diverse variables, among others, by

Glasner, Barret, Thomson and Rochelle with different results due to different measuring devices, time measurement, and control of confounding variables. Baret et al, in a cross-sectional study in 796 primiparous women for over 6 months, found 62% had dyspareunia in the first 3 months post-delivery, 31% at 6 months postdelivery, and 12% in the first year. Sexual desire disorder was found in 53% of women in the first 3 months, 37% at 6 months and 9% in the first year. As for the disturbance to reach orgasm was identified in 33% of women in the first 3 months, 23% within the first 6 months, and 14% in the first year.[1,2-4]

This study is carried out because there is an absence of data on sexual dysfunction 3 months postdelivery in spontaneous labor and cesarean section in Jakarta and Indonesia, as well as a confirmation of the existing research. We aim to study the comparison of encouragement, stimuli, orgasm, pain and satisfaction of female sexual function at 3 months postpartum between spontaneous delivery and cesarean section in Dr. Cipto Mangunkusumo Hospital in Jakarta.

**Table 1.** Characteristic of Respondents

| Characteristics | Total (n=150) | Spontaneous (n=75) | C-Section (n=75) | p |
|---|---|---|---|---|
| **Age, Median Cluster of age, n (%)** | 30 (25-33) | 30 (25-35) | 31 (26-34) | 0.211 |
| <20 years | 9 (6.0) | 5 (6.7) | 4 (5.3) | 0.210 |
| 20-30 years | 72 (48.0) | 42 (56.0) | 30 (40.0) | |
| 31-40 years | 63 (42.0) | 24 (32.0) | 39 (52.0) | |
| >40 years | 6 (4.0) | 4 (5.3) | 2 (2.7) | |
| **Level of Education, n (%)** | | | | |
| Elementary | 45 (30.0) | 22 (29.3) | 23 (30.7) | 0.904 |
| Advanced | 81 (54.0) | 40 (53.3) | 41 (54.7) | |
| University/college | 24 (16.0) | 13 (17.3) | 11 (14.7) | |
| **Working Statue, n (%)** | | | | |
| Yes | 94 (62.7) | 49 (65.3) | 45 (60.0) | 0.500 |
| No | 56 (37.3) | 26 (34.7) | 30 (40.0) | |
| **Parity, n (%)** | | | | |
| Primipara | 58 (38.7) | 29 (38.7) | 29 (38.7) | 1.000 |
| Multipara | 87 (58.0) | 44 (58.7) | 43 (57.3) | |
| Grande multipara | 5 (3.3) | 2 (2.7) | 3 (4.0) | |
| **Average Baby Weight (gr)** | 2900 | 3020 | 2800 | 0.026 |
| **Baby Weight Range** | (2600-3200) | (2800-3250) | (2600-3100) | |
| **Cluster Baby weight, n (%)** | | | | |
| <2500 gram | 14 (9.3) | 7 (9.3) | 7 (9.3) | 1.000 |
| 2500-4000 gram | 132 (88.0) | 67 (89.3) | 65 (86.7) | |
| >4000 gram | 4 (2.7) | 1 (1.3) | 3 (4.0) | |
| **Perineal Tear Degree** | | | | |
| No Tear | 93 (62.0) | 18 (12.0) | 75 (0.0) | <0.001 |
| Grade I (Light) | 7 (4.7) | 7 (4.7) | 0 (0.0) | |
| Grade II (Moderate) | 43 (28.7) | 43 (28.7) | 0 (0.0) | |
| Grade III-IV (Heavy) | 7 (4.7) | 7 (4.7) | 0 (0.0) | |
| **Breastfeeding Status** | | | | |
| Yes | 130 (86.6) | 62 (82.7) | 68 (90.7) | <0.001 |
| No | 20 (13.3) | 13 (17.3) | 7 (9.3) | |
| **Start of Sexual Intercourse** | | | | |
| Within 40 day | 138 (92.0) | 69 (92.0) | 69 (92.0) | 1.000 |
| 2 months | 6 (4.0) | 4 (5.3) | 2 (2.7) | |
| 3 months | 6 (4.0) | 2 (2.7) | 4 (5.3) | |

## METHOD

We carried out an observational study measuring sexual function 3 months post-delivery using the Female Sexual Function Index (FSFI) questionnaire, with a cross-sectional study design and consecutive sampling.

Analysis for post-delivery female sexual function based on the method of delivery (spontaneous labor or cesarean section) was carried out using Chi-square or Fisher test. Analysis of confounding variables (parity, age, education, parity and degree of perineal laceration) was done by multivariate logistic regression.

## RESULT

We included 150 subjects in our study, 75 subjects in each group of spontaneous labor and cesarean section. The characteristics of our respondents are presented in Table 1.

From 150 respondents, 43.3% had sexual dysfunction, with 52% of the spontaneous labor group and 34% of the cesarean section group. Bivariate analysis showed that occurrence of sexual dysfunction at three months post-spontaneous labor was 1.5 times higher (95% CI 1.02-3.19) compared with cesarean section. Sexual encouragement shows a two-fold difference (95% CI 1.17-3.40) compared to cesarean section. However, orgasm disturbance was 8 times higher (95% CI 1.90-3.58) in the spontaneous labor group, with confounding variable of perineal rupture. Disturbance of sexual stimuli, satisfaction, and pain were not significantly different between spontaneous labor and cesarean section.

**Table 2.** The Relationship between Sexual Dysfunction and Various Variables

| Variables | Sexual Function | | | | p | RR | 95% CI |
|---|---|---|---|---|---|---|---|
| | Dysfunction | | Normal | | | | |
| | N | % | N | % | | | |
| **Mode of Delivery** | | | | | | | |
| Spontaneous labor | 39 | 52.0 | 36 | 48.0 | 0.032 | 1.500 | 1.027-2.192 |
| Cesarean section | 26 | 34.7 | 49 | 65.3 | | | |
| **Age** | | | | | | | |
| <20 year | 2 | 22.2 | 7 | 77.8 | 0.716 | 0.934 | 0.648-1.374 |
| 20-30 year | 32 | 44.4 | 40 | 55.6 | | | |
| 31-40 year | 27 | 42.9 | 36 | 57.1 | | | |
| >40 year | 4 | 66.7 | 2 | 33.3 | | | |
| **Education Level** | | | | | | | |
| Elementary | 21 | 46.7 | 24 | 53.3 | 0.590 | 1.114 | 0.758-1.637 |
| Advanced | 35 | 43.2 | 46 | 56.8 | | | |
| University | 9 | 37.5 | 15 | 62.5 | | | |
| **Parity** | | | | | | | |
| Primipara | 24 | 41.4 | 34 | 58.6 | 0.701 | 0.929 | 0.634-1.360 |
| Multipara (2-4) | 36 | 41.4 | 51 | 58.6 | | | |
| Grande Multipara (≥ 5) | 5 | 100.0 | 0 | 0.0 | | | |
| **Perineal Tear Degree** | | | | | | | |
| No tear | 37 | 39.8 | 56 | 60.2 | 0.415 | 0.854 | 0.589-1.239 |
| Light | 4 | 57.1 | 3 | 42.9 | | | |
| Moderate | 21 | 48.8 | 22 | 51.2 | | | |
| Severe | 3 | 42.9 | 4 | 57.1 | | | |
| **Breast Feeding** | | | | | | | |
| Yes | 58 | 44.6 | 72 | 55.4 | 0.419 | 1.275 | 0.681-2.387 |
| No | 7 | 35.0 | 13 | 65.0 | | | |

**Table 3.** Multivariate Analysis of Factors that Affect Sexual Desire Dysfunction

| Variables | B | S | E Wald | p-value | R | 95% CI |
|---|---|---|---|---|---|---|
| Spontaneous Delivery | 0.999 | 0.377 | 7.041 | 0.008 | 2.716 | 1.298 - 5.682 |
| Multiparity | 0.643 | 0.393 | 2.681 | 0.102 | 1.903 | 0.881 - 4.111 |
| Constant | -1.810 | 0.401 | 20.352 | <0.001 | 0.164 | |

Multivariate analysis found that spontaneous labor was statistically significant for sexual dysfunction at three months post-delivery in patients with sexual encouragement (RR=2.716, p=0.008) and orgasm accession dysfunction (RR=6.952, p=0.031). However, the more than 30 years old of age variable was statistically significant in sexual dysfunction variable with RR=2.60 and p=0.021.

## DISCUSSION

Spontaneous labor often have complications such as laceration of the birth canal, and is considered to affect the occurrence of post-delivery sexual dysfunction compared to cesarean section.[5] The comparative data on the presence of female sexual function 3 months post-delivery with spontaneous labor and cesarean section in Indonesia in detail, with control of confounding variables and adequate number of samples are the advantages of this study, while the drawback is the collection of data by telephone interview resulting in a lack of data accuracy and the possibility of bias. Most respondents (92%) have resumed sexual activity at 40 days post-delivery, only 4% who had sexual intercourse with her partner after 2 months post-delivery by reason of fear of pain because of the IUD, perineal sutures on spontaneous labor, as well as the fear of opening the surgical wounds in cesarean section. This is consistent with the Barret study, which found that 89% of women have begun sexual activity at three months post-delivery, and there was no significant difference in the return of sexual relationship between cesarean section with spontaneous labor.[6] The reasons given for delaying sexual intercourse are concern about perineal pain, bleeding and fatigue.

The best suggestion regarding when to start intercourse is based on the desire and comfort of the patient.[2] Three months post-delivery, 43.3% experienced sexual dysfunction with a ratio of 52% in spontaneous delivery and 34% in cesarean section. With the highest domain being sexual desire (40%) in spontaneous labor and pain during sexual intercourse (24%) in the cesarean section, followed by sexual arousal dysfunction, orgasm, lubrication, and sexual satisfaction. Buhling et al, in a cross-sectional study in 796 primiparous women for over 6 months, found 62% had dyspareunia in the first 3 months post-delivery, 31% at 6 months post-delivery, 12% in the first year. For sexual desire disorder, it was obtained that 53% had experienced this in the first 3 months, 37% at 6 months and 9% in the first year. It was also found that 33% experienced disturbance to reach orgasm in the first 3 months, 23% within the 6 months, and 14% in the first year.[1,7] Post-delivery sexual function can be affected by several factors, such as injury to the perineum, pudendal neuropathy, vaginal dryness due to breastfeeding, to changes in relationships, function and lifestyle. It is widely reported that mode of delivery affect post-delivery sexual function, with the incidence of injury to the birth canal in vaginal delivery said to be one of the main factors of sexual dysfunction post-delivery.[3] In bivariate analysis, disruptions of sexual desire in 3 months post-spontaneous delivery was 2 times greater (95%CI 1.17-3.40) compared to cesarean section, while disruption of orgasm was 8 times greater (95%CI 1.90-3.58) with the presence of perineal laceration as confounding variable. Sexual dysfunction at 3 months post-spontaneous delivery has been found to be 1.5 times greater (95%CI 1.02-2.19) compared to cesarean section.

In theory, sexual desire disorder is a spectrum of disease that causes personal suffering due to loss of sexual fantasies and desire that persists or recurs, and the lack of response to sexual activity. This condition can be caused by menopause due to medical reasons, depression, endocrine disorders, prolonged conflict, psychological or emotional problems, childhood trauma, and physical or sexual abuse. Sexual arousal disorder is the persistent or recurrent inability to obtain or maintain adequate sexual pleasure, lack of subjective pleasure, lack of somatic responses, lack of genital lubrication or swelling, which may be caused by nerve damage after surgery, organic causes in the pelvic area which may decrease

sensation in the labia and clitoris, as well as lack of vaginal smooth muscle relaxation. Other causes are generally psychological. Disorders of orgasm may be complete loss or recurrent difficulty in achieving orgasm after sufficient stimulation, usually caused by emotional trauma or sexual abuse, hormone deficiency, trauma due to surgery, or treatment using SSRIs (selective serotonin reuptake inhibitors).[3,8]

At the age of more than 40 years old, is the perimenopausal period; the period in which changes occur in the organs involved in the acceptance of sexual stimulation. Decreased activity of the sweat and oil glands results in decreased touch sensation, while a decrease in fat leads to less optimal breast engorgement and nipple erection in response to sexual stimulation. In addition, the vagina shortens and loses its elasticity, physiological secretion of mucus (lubrication) of the wall of the vagina and cervix is decreased.[3,9,10] In this study, it was found that age is significantly associated with the sexual generation, where increasing age is related with decreased sexual desire (RR=0.52).

Fajewonyomi et al discovered that sexual dysfunction is more commonly experienced by Nigerian women with higher levels of education, with the explanation that women with higher education levels have higher awareness regarding health issues and more open in discussing sexual issues.[4] In this study, education level is associated with impaired lubrication, where the education level is inversely related with the presence of lubrication disorders (RR=2.33). In contradiction, Rosen et al observed that higher education levels is associated with a lower incidence of sexual dysfunction.[8]

Number of parity and degree of perineal tear are associated with pelvic floor muscle function, which affects the onset of sexual dysfunction after delivery.[5,9] In this study, parity was not statistically correlated to sexual function, whereas degree of perineal laceration influences orgasm disorder, where the degree of perineal laceration is inversely related to orgasm disorder (RR=0.25). Signorello observed that, in the United States, second-degree perineal laceration, with or without episiotomy, increases the incidence of dyspareunia at 3 months post-delivery. Meanwhile, Rogers et al discovered that in labor with spontaneous birth canal injury (without episiotomy), there is no difference in terms of sexual activity and short-term post-delivery sexual function at a low degree perineal laceration (without trauma to degree I) as well as a high degree (degree II-IV).[5]

Breastfeeding is one of the factors that play a role in the occurrence of post-delivery sexual dysfunction. High levels of prolactin cause the levels of estrogen, progesterone and androgens to be decreased, resulting in a decrease of vaginal secretions and the tendency for depressive mood. This can cause sexual pain disorder and lack of interest or sexual desire, as stated by Masters and Johnson.[11] Actively lactating women have high levels of sexual activity and higher desire to be sexually active, due to the increase in breast eroticism and baby sucking activity. On the other hand, lower sexual activity may be experienced due to breast pain, post-delivery pain, decreased secretion of breast milk and vaginal discharge. In this study, breastfeeding variable was not significantly associated with the occurrence of sexual dysfunction.[12]

Multivariate analysis found that spontaneous labor was statistically significant with the occurrence of sexual dysfunction 3 months post-delivery in sexual arousal dysfunction and achieving orgasm variables, with p=0.008 and p=2.716, while the variable of age being over 30 years old is a significant confounding variable in the occurrence of sexual dysfunction in sexual desire variables (p=0.021). Spontaneous labor variables and age over 30 years are statistically influential variables on sexual dysfunction 3 months post-delivery, whereas the other variables either cesarean section, breastfeeding, working or not, the level of education and degree of perineal laceration was not statistically significant for sexual function. Kapllan stated that women's sexual response is much more complex, involving social, psychological, neurological, vascular and hormonal factors, as well as its interaction with sexual stimulation, central and peripheral nervous systems not being fully understood yet. WHO defines sexual health as the integration of somatic, emotional, intellectual and social aspects in ways that enrich and add to the quality of personality, communication and love.[13]

## CONCLUSION

Almost all respondents have resumed sexual activity at 40 days post-delivery with spontaneous labor or cesarean section, and only few have not started their sexual activity after 3 months post-delivery. The prevalence of sexual dysfunction 3 months post-delivery was 52% in spontaneous labor and 34% in cesarean section, with the highest domain in sexual arousal, pain during sexual intercourse, sexual desire,

lubrication, orgasm disorders, and sexual satisfaction. In spontaneous labor, sexual dysfunction, sexual desire disorder, orgasm disturbances at 3 months post-delivery is greater in spontaneous labor compared to cesarean section, with the presence of perineal laceration as confounding variable. Multivariate analysis of spontaneous labor variable was statistically significant for sexual dysfunction in patients 3 months post-delivery for sexual arousal dysfunction and achieving orgasm variables, while the over 30 years of age variable was significantly influential to the sexual dysfunction variable.

Counseling is required for women, considering the high prevalence of post-delivery sexual dysfunction at 3 months post-delivery. To reduce sampling bias research should be done by direct interviews or home visits, as well as the variable of cesarean section should include patient having elective cesarean.

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Research Article

# Diagnostic Value of IGFBP-1 Rapid Test and Combined IGFBP-1-AFP in Vaginal Fluid from Premature Rupture of Amniotic Membranes

## *Nilai Diagnostik Insulin-like Growth Factor Binding Protein 1 (IGFBP-1) dan Kombinasi IGFBP-1-alpha-fetoprotein (IGFBP-1-AFP) di Cairan Vagina pada Kejadian Ketuban Pecah Prematur*

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## Abstract

**Objective:** To compare the diagnostic value of IGFBP-1 and combined IGFBP-1-AFP rapid tests in diagnosing premature rupture of membranes (PROM).

**Method:** This study was conducted in Dr. Soetomo Hospital in Surabaya from July to November 2013. The subjects were 52 pregnant women with presumed PROM diagnosis, which was recorded by clinical data and sampling of vaginal discharge swab. The diagnostic value was obtained by comparing the results of IGFBP-1 and combinated IGFBP-1-AFP rapid tests by standard PROM examination namely vaginal pooling, litmus paper test and ferning test.

**Result:** A difference between the diagnostic value of IGFBP-1 and combined IGFBP-1-AFP rapid tests in diagnosing PROM was shown, where the sensitivity and specificity of IGFBP-1 rapid test was 85% and 95%, compared to combined IGFBP-1-AFP rapid test, which was 91% and 95%. The correlation coefficient of combined IGFBP-1-AFP rapid test with standard PROM examination (r=0.841, p=0.000) was higher than the correlation coefficient of IGFBP-1-AFP rapid test with standard PROM examination (r=0.772, p=0.000).

**Conclusion:** Combined IGFBP-1-AFP rapid test has a better diagnostic value than IGFBP-1 rapid test alone.

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**Keywords:** combined IGFBP-1-AFP, IGFBP-1, PROM

## *Abstrak*

***Tujuan:*** *Mengetahui perbandingan nilai diagnostik rapid test IGFBP-1 dan kombinasi IGFBP-1-AFP dalam mendiagnosis KPP.*

***Metode:*** *Penelitian ini dilakukan di RSUD Dr. Soetomo Surabaya sejak Juli sampai November 2013. Subjek penelitian adalah 52 ibu hamil dengan dugaan diagnosis KPP, dicatat data klinisnya dan dilakukan pengambilan sampel swab cairan vagina. Nilai diagnostik diperoleh dengan membandingkan hasil rapid test IGFBP-1 dan kombinasi IGFBP-1-AFP dengan pemeriksaan standar KPP, yaitu vaginal pooling, tes kertas lakmus dan tes ferning.*

***Hasil:*** *Terdapat perbedaan antara nilai diagnostik rapid test IGFBP-1 dan kombinasi IGFBP-1-AFP dalam mendiagnosis KPP, yaitu sensitivitas dan spesifisitas rapid test IGFBP-1 ditemukan 85% dan 95%, dibandingkan kombinasi IGFBP-1-AFP yaitu 91% dan 95%. Koefisien korelasi rapid test IGFBP-1 dengan pemeriksaan standar KPP (r=0,772, p=0,000) lebih besar dibandingkan koefisien korelasi rapid test kombinasi IGFBP-1-AFP dengan pemeriksaan standar KPP (r=0,841, p=0,000).*

***Kesimpulan:*** *Rapid test kombinasi IGFBP-1-AFP mempunyai nilai diagnostik yang lebih baik dibandingkan rapid test IGFBP-1 saja.*

*[Maj Obstet Ginekol Indones 2015; 3: 133-139]*

***Kata kunci:*** *IGFBP-1, kombinasi IGFBP-1-AFP, KPP*

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## INTRODUCTION

A Prelabor or Premature Rupture of Amniotic Membranes (PROM) is defined as a condition of spontaneous ruptured membranes within 1 hour or more before the onset of labor, as indicated by general symptoms such as a large discharge of vaginal fluid. Differential diagnosis of this condition is excessive urinary incontinence, vaginal mucus for physiological or pathological causes, and cervical mucus during the labor process.[1,2]

The incidence of PROM is relatively high, reaching 10-12% of all pregnancies, making it the major cause of premature childbirth in the United States of America. The leaking of amniotic fluids is also related to increased infection in the mother and baby, which is the the primary cause of infection to both the mother and baby.[3]

PROM diagnosis is always established through anamnesis, clinical examination and vaginal speculum examination. A standard examination for PROM diagnosis is the existence of vaginal pooling in vaginal speculum examination, litmus paper test and ferning body in microscopic examination of vaginal fluid. A small amount of fluid or leakage of vaginal fluid in several cases makes PROM difficult to detect, and the pregnant women rarely realizes it. The pregnant women always fail to differ whether the vaginal discharge is amniotic fluid, urine or mucus. Clinicians have experienced difficulty to establish a diagnosis only based on anamnesis, clinical examination and vaginal speculum examination in as much as 47% of PROM cases.[2,4] The standard examination for detecting leaked amniotic fluid always raised doubt in clinicians regarding establishing the PROM diagnosis, so that many researchers have ventured to find a more objective test.

Amniotic fluid detection may be conducted through immunology testing to detect the molecules existing in high-concentration in the amniotic fluid; such as fibronectin, insulin-like growth factor binding protein-1 (IGFBP-1), alpha-fetoprotein (AFP) and others. This reasearch aims to identify and compare the diagnostic value of IGFBP-1 and combined IGFBP-1-AFP in the amniotic fluid with standard PROM examination, such as vaginal pooling examination using vaginal speculum, vaginal fluid's pH examination using litmus paper test, and ferning body examination with vaginal fluid microscopy for PROM diagnosis.

## METHOD

This is an observational-analytic research with a cross-sectional approach. It was conducted at the Department of Clinical Pathology, Faculty of Medicine, Airlangga University, and the delivery room and maternity outpatient clinic of Dr. Soetomo Hospital, Surabaya starting from July to November 2013.

The subjects of this research were pregnant women visiting the delivery room of Dr. Soetomo Hospital, Surabaya with complaints of vaginal fluid discharge who met the criteria of subject acceptance and rejection criteria to conduct amniotic fluid examination using *Amnioquick* (IGFBP-1) and *Amnioquick Plus 2* (combined IGFBP-1-AFP) *rapid tests* until the maximum sample was fulfilled. The inclusion criteria were second and third trimester pregnant women complaining of fluid leakage or discharge. The exclusion criteria was presence of vaginal bleeding. The minimum number of subjects based on sample calculation was 36 patients.

Sampling was conducted during the patients' visit to the delivery room of Dr. Soetomo Hospital. We obtained 52 samples with complaints of vaginal fluid discharge in 5 months starting from July to November 2013.

To perform the assessment, the research subject was placed in the lithotomy position. A sterile and disposable vaginal speculum was then placed in the vagina and presence of vaginal pooling was observed in the posterior fornix. A red litmus paper was contacted with the fluid existing in the posterior fornix; and if the color turned blue, it was evident that it was amniotic fluid. A vaginal sample was taken with a sterile and disposable swab from the posterior fornix area. The vaginal fluid swab was conducted 3 times; the first swab was for *Amnioquick Plus 2 rapid test* examination, the second was for *Amnioquick rapid test* and the third was for a ferning test. The vaginal fluid swab for the *Amnioquick rapid test* and *Amnioquick Plus 2* examinations was kept for about 1 minute. The examination to observe the existence of ferning body was conducted by dropping vaginal secretion or spreading vaginal fluid on an object glass which was kept until dry. The microscopy examination was performed using a microscope with 100x magnification, which would display fern pattern showing the indication of amniotic fluid and PROM.

The examinations with *Amnioquick* and *Amnioquick Plus 2 rapid tests* were conducted by dipping a vaginal fluid swab in a buffer solution for about 10 seconds. The test strip was put in the buffer solution with arrow mark at strip test directed to the bottom and the strip touching the bottom of the buffer solution vial. The test strip was kept for about 10 minutes in the buffer solution. The result of *Amnioquick* and *Amnioquick Plus 2 rapid tests* may be interpreted after the 10 minutes. The appearance of a purple/pink control line on the test strip showed that the procedure was conducted correctly. The test result was not allowed to be interpreted after more than 15 minutes after the test strip was in the buffer solution. The *Amnioquick Plus 2* examination was conducted almost at the same time with *Amnioquick* examination. The interpretation result of *Amnioquick Plus 2* showed 3 categories, which were positive, negative and doubtful. For the interest of analysis, the interpretation of *Amnio-*

*quick Plus 2* was changed to 2 categories, namely positive and negative. There were 3 subjects showing a doubtful result. The three research subjects were then observed further into the labor period, and based on diagnosis upon leaving the hospital, the subjects were entered into categories of positive result of *rapid test Amnioquick Plus 2* examination.

The collected data were coded, tabulated, and entered into the computer. A categorical-scale variable such as age, gestational age, diagnosis and other variables were then presented as frequency and percentage distribution. Diagnostic values (sensitivity, specificity, positive predictive value, negative predictive value, diagnostic efficiency, positive likelihood ratio and negative likelihood ratio) were calculated using a 2 x 2 table.

The standard examination conducted for determining PROM diagnosis was based on at least 2 positive examination results of either the existence of vaginal pooling in vaginal speculum examination, positive litmus paper test, the existence of ferning body in the vaginal secretion microscopic examination and the existence of certain substance in the amniotic fluid which may be detected by *rapid test*.[5,6] The confidentiality of the patients was protected by changing subjects' name with a code/initial or number; and all patients' data and anything related to this research would be treated as confidential. This research has obtained ethical approval from the Ethical Team of Dr. Soetomo Hospital, Surabaya.

## RESULTS

The total number of pregnant women receiving standard examination was 52 subjects, consisting of 33 PROM pregnant women, and 19 non-PROM pregnant women. Data concerning the characteristics of our subjects can be seen in Table 1.

The average age of the PROM group was 28.70 years old, with a range from 20 to 40 years old. Meanwhile, the average age of the non-PROM group was 28.68 years old with a range from 19 to 41 years. The average gestational age of the PROM pregnant women was 35.64 weeks, with a range of 27 to 40 weeks; while for the non-PROM pregnant women was 32.89 weeks, with a range of 20 to 40 weeks. The average parity was 2 in the PROM group and 1.84 in the non-PROM group. The average estimated fetal weight for the PROM group was 2,530.30 gram with a range of 1,000 to 3,500 gram. The average estimated fetal weight of the non-PROM group was 1,873.68 gram with a range of 900 to 3,600 gram. The fundal height for the PROM group was 29.33 cm in average, while it was averaged to be 26 cm for the non-PROM group. There was no significant difference in the maternal age, gestational age, parity, estimated fetal weight and fundal height between the PROM and non-PROM group ($p > 0.05$). This indicated that both groups were homogeneous based on those aspects.

**Table 1.** Characteristics of Research Samples

| Characteristics | PROM (n=33) | | Non-PROM (n=19) | | *p*-value |
|---|---|---|---|---|---|
| | Range | Average ± SD | Range | Average ± SD | |
| Age (years) | 20-44 | 28.70 ± 5.14 | 19-41 | 28.68 ± 6.74 | 0.99 |
| Gestational age (weeks) | 27-40 | 35.64 ± 3.83 | 20-40 | 32.89 ± 4.99 | 0.61 |
| Parity | 1-5 | 2.03 ± 1.35 | 1-4 | 1.84 ± 0.89 | 0.59 |
| Estimated fetal weight (gram) | 1000-3500 | 2530.30 ± 810.66 | 900-3600 | 1873.68 ± 879.92 | 0.09 |
| Fundal height (cm) | 21-36 | 29.33 ± 4.56 | 18-35 | 26 ± 4.77 | 0.16 |

**Table 2.** The Results of *Amnioquick rapid test* and *Amnioquick Plus 2* Examination in the PROM and Non-PROM Groups

| Examination | PROM (n=33) | | Non-PROM (n=19) | |
|---|---|---|---|---|
| | True Positive (%) | False Negative (%) | False Positive (%) | Negative (%) |
| Amnioquick | 28 (84.8) | 5 (15.2) | 1 (5.3) | 18 (94.7) |
| Amnioquick Plus 2 | 30 (90.9) | 3 (14.3) | 1 (5.3) | 18 (94.7) |

The examination by *Amnioquick rapid test* showed no invalid result. The results of *Amnioquick rapid test* examination in PROM pregnant women showed a true positive for 28 women (84.8%) and false negative for 5 women (15.2%). The *Amnioquick rapid test* examination in non-PROM pregnant women showed negative for 18 women (94.7%) and false positive for 1 woman (5.3%).

The result of *Amnioquick Plus 2 rapid test* examination in PROM showed a true positive for 30 cases (90.9%) and false negative for 3 cases (14.3%). The *Amnioquick Plus 2 rapid test* examination in non-PROM pregnant women showed negative for 18 cases (94.7%) and false positive for 1 case (5.3%).

The diagnostic value of *Amnioquick rapid test* to detect PROM diagnosis showed an 85% sensitivity, 95% specificity, 97% positive predictive value, 78% negative predictive value, 86.8% diagnostic efficiency, 16.12 positive likelihood ratio and 0.16 negative likelihood ratio.

The diagnostic value of *Amnioquick Plus 2 rapid test* to detect PROM showed a 91% sensitivty, 95% specificity, 97% positive predictive value, 86% negative predictive value, 92.3% diagnostic efficiency, 17.27 positive likelihood ratio and 0.10 negative likelihood ratio.

*Amnioquick Plus 2* was found to have a higher sensitivity, negative predictive value, diagnostic efficiency and positive likelihood ratio than the *Amnioquick rapid test*. The specificity and negative predictive value of *Amnioquick* and *Amnioquick Plus 2* was similar (95% and 97%), while the negative likelihood ratio of *Amnioquick Plus 2* was lower than *Amnioquick*.

The examination using *Amnioquick rapid test* showed a significant correlation at r=0.772 (p=0.000) when related to standard PROM examination. Likewise, the examination using *Amnioquick Plus 2 rapid test* showed a significant correlation at r=0.841 (p=0.000) when related to standard PROM examination. However, the correlation coefficient value of *Amnioquick Plus 2* was higher than the *Amnioquick*.

## DISCUSSION

PROM is often related to the morbidity of maternal and perinatal infection. Clinicians need to consider whether pregnancy will be maintained or not based on the possible risks for the mother and fetus in the management of PROM. The failure to establish PROM diagnosis may lead to the misapplication of standard PROM managements. On the contrary, an inappropriate PROM diagnosis establishment may cause mismanagement such as unnecessary hospitalization and labor induction. The establishment of PROM diagnosis is very important to avoid serious complications to the mother and fetus.[7-9]

Clinical diagnosis of PROM can simply be established if the pregnant woman complained of significant discharge of vaginal fluid or fluid leaking from the vaginal cervix. Clinicians are still doubting the establishment of PROM diagnosis based on anamnesis and speculum examination in 47% of cases. The PROM diagnosis is hard to establish if the vaginal discharge is little or only leaking. Another noninvasive examination may be needed to establish PROM diagnosis.[4,10] In our study, the subjects were divided into 2 groups, namely the PROM and the non-PROM group. There was no significant differ-

**Table 3.** The Diagnostic Value of *Amnioquick* and *Amnioquick Plus 2* with Standard PROM Examination in PROM

| Diagnostic Test | Amnioquick | 95% Confidence Interval | Amnioquick Plus 2 | 95% Confidence Interval |
|---|---|---|---|---|
| Sensitivity | 85 % | 73 - 97 % | 91 % | 81 - 100 % |
| Specificity | 95 % | 85 - 100 % | 95 % | 85 - 100 % |
| Positive predictive value | 97 % | 90 - 100 % | 97 % | 91 - 100 % |
| Negative predictive value | 78 % | 61 - 95 % | 86 % | 71 - 100 % |
| Diagnostic efficiency | 86.8 % | - | 92.3 % | - |
| Positive likelihood ratio | 16.12 | 2.38 - 109.21 | 17.27 | 2.56 - 116.73 |
| Negative likelihood ratio | 0.16 | 0.07 - 0.36 | 0.10 | 0.03 - 0.28 |

ence between both groups in terms of the maternal age, gestational age, parity, estimated fetal weight, and the fundal height, so that the both groups could be considered as homogeneous.

The IGFBP-1 detection in the vaginal fluid using *Amnioquick rapid test*, which is considered a one-step bedside test, was deemed to produce a better sensitivity and specificity. Vaginal infections, medications, urine or seminal fluid show no effect on *Amnioquick rapid test*, unlike in litmus paper test. In this study, the false positive value of *Amnioquick rapid test* was 5.3%, compared to the previous research of 17.3%. Excessive vaginal bleeding may contribute to more positive result due to the IGFBP-1 which can also be found in blood.[11,12]

The IGFBP-1 level is generally equal in the cervical and vaginal fluid in the first trimester of pregnancy, but the IGFBP-1 level in the cervical fluid is two-times higher than the vaginal fluid in the second trimester. This implicates that the sampling site has an effect on the IGFBP-1 level in the genital tract if a swab is used in the sampling process. The *Amnioquick rapid test* showed a false negative of 15.2%, compared to the false negative number of 10.7% of IGFBP-1 in the previous research. This may be attributable to the inaccurate sampling site of vaginal swab, which should ideally be in the posterior vaginal fornix.[13,14]

The use of IGFBP-1 and AFP combination in a kit (*Amnioquick Plus 2*) is intended to increase the sensitivity and specificity. The IGFBP-1 line is set on a lower sensitivity to detect IGFBP-1 at a level of 10 ng/ml in order to produce a higher specificity. The AFP line is set on a higher sensitivity to detect AFP level of 5 ng/ml, allowing for a more sensitive and specific result at a gestational age of more than 38 weeks. The IGFBP-1 becomes less specific and the AFP becomes more specific when the pregnancy is after 38 weeks due to increasing IGFBP-1 level along with cervical maturation, resulting in a false positive result. This was concordant with the result of this research, where false positive value of *Amnioquick Plus 2 rapid test* was found to be low (5.3%). As noted previously, the false positive result can also be caused by blood. In this study, the false negative result of *Amnioquick Plus 2 rapid test* was 14.8% which may be caused by the less-appropriate sampling site of vaginal swab, the long time lapse between sampling and the time amniotic membrane was ruptured (more than 12 hours) so that the flow of amniotic fluid have stopped, and the declining AFP level in the amniotic fluid during pregnancy at an age of more than 39 weeks.[15,16]

In this study, *Amnioquick rapid test* was more sensitive and specific in diagnosing PROM compared to the litmus paper test and ferning test. The sensitvity and specificity of *Amnioquick rapid test* was 85% and 95%, respectively. The sensitivity and specificity of *Amnioquick rapid test* was better than that of the litmus paper test (88% dan 74%, respectively) and ferning test (82% and 95%, respectively). The positive predictive value and negative predictive value of *Amnioquick rapid test* was 97% and 78%, better than the positive predictive value and negative predictive value of the litmus paper test (85% and 78%, respectively) and ferning test (96% and 75%, respectively). The positive likelihood ratio of the *Amnioquick rapid test* was 16.12, while the litmus paper test was 3.34, and ferning test was 15.55, which means that the examination showed a possible PROM diagnosis result respectively at 16.12 times, 3.34 times and 15.55 times compared to non-PROM. The negative likelihood ratio of the *Amnioquick rapid test* was 0.16, the litmus paper test 0.16 and the ferning test 0.19.

Dilbaz et al found that the sensitivity of IGFBP-1 in detecting PROM was 88%, with 81% specificity, 79% positive predictive value and 90% negative predictive value. They concluded that the IGFBP-1 strip test is a reliable test in diagnosing PROM, even for preterm PROM cases, as well as for confirming clinical diagnosis.[12]

Erdemoglu et al stated that the IGFBP-1 detection test has a sensitivity equal to the litmus paper test (97%) but was more specific (97% vs 16%) and accurate (97% vs 56%) in diagnosing PROM. Another research showed that in several cases, the diagnosis of PROM is hard to establish in a clinical way and the IGFBP-1 examination in the cervical and vaginal secretion using a dipstick quick test showed a sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 92%, 84%, and 100%, respectively.[11,17]

The IGFBP-1 concentration in amniotic fluid is 100 to 1000 times higher than in serum. The *Amnioquick rapid test* relies on immunochromatography (ICT) with the principle of using monoclonal antibody against the human IGFBP-1. The *Amnioquick rapid test* shows a positive result for PROM if the sample contains at least 10 ng/ml IGFBP-1, so that it will give a more specific result. This is in accordance with our result, which shows a high specificity value of *Amnioquick rapid test* (97%).

In this study, the *Amnioquick Plus 2 rapid test* is more sensitive and specific in diagnosing PROM compared to the litmus paper test and ferning test. The sensitivity and specificity of *Amnioquick Plus 2 rapid test* was 91% and 95%, respectively, higher than the sensitivity and specificity of the litmus paper test and ferning test. The positive predictive value and negative predictive value of *Amnioquick Plus 2 rapid test* was 97% and 86% respectively, also higher than the positive predictive value and negative predictive value of litmus paper test and ferning test. The positive predictive value of *Amnioquick Plus 2 rapid test* was 97%, meaning that if the test shows a positive result, it will predict 97% of PROM. The negative predictive value of *Amnioquick Plus 2 rapid test* is also very useful for screening, which means that if the result using *Amnioquick Plus 2 rapid test* was negative, it will predict 86% of non-PROM.

The PROM diagnosis by ICT method to detect AFP has an accuracy of 97.8%, sensitivity of 97.9% and specificity of 97.8%. Another research showed that using a dipstick test to detect IGFBP-1 and AFP combination in the vaginal fluid had a sensitivity and specificity of 90.91%, and 97.10%, respectively. This was almost the same with the result using *Amnioquick Plus 2 rapid test* in our study.[18,19]

The sensitivity and specificity of *Amnioquick Plus 2 rapid test* is higher than that of the *Amnioquick rapid test* because the *Amnioquick Plus 2* uses two indicators namely IGFBP-1 and AFP. The IGFBP-1 is more specific in detecting PROM in gestational age of less than 38 weeks, meanwhile the AFP is more specific in detecting PROM in gestational age of more than 38 weeks making up for the increasing level of IGFBP-1 in the vaginal fluid as the cervix matures, which may give a false positive result.

The higher sensitivity and specificity of *Amnioquick* and *Amnioquick Plus 2 rapid tests* may assist in establishing the PROM diagnosis, especially in cases where the diagnosis is doubtful. The examination using *Amnioquick* and *Amnioquick Plus 2 rapid tests* should follow the procedure in the kit guidelines in order to minimize the possibility of false positive and false negative results.

The *Amnioquick* and *Amnioquick Plus 2 rapid tests* both have a strong and significant correlation with standard PROM examination. In our study, the *Amnioquick*, *Amnioquick Plus 2 rapid test*, and standard PROM examination are conducted on the same subjects so that the correlation coefficient can be comparable. The correlation coefficient of *Amnioquick Plus 2* is higher than the *Amnioquick rapid test*. Thus, it can be stated that the *Amnioquick Plus 2 rapid test* is better than the *Amnioquick rapid test*, such being our hypothesis in this study.

## CONCLUSION

The *Amnioquick rapid test* compared to the standard PROM examination has an 85% sensitivity, 95% specificity, 97% positive predictive value, 78% negative predictive value, 86.8% diagnostic efficiency, 16.12 positive likelihood ratio, and 0.16 negative likelihood ratio. The *Amnioquick Plus 2 rapid test*, compared to the standard PROM examination, has a 91% sensitivity, 95% specificity, 97% positive predictive value, 86% negative predictive value, 92.3% diagnostic efficiency, 17.27 positive likelihood ratio, and 0.10 negative likelihood ratio. The correlation of *Amnioquick Plus 2* to the standard PROM examination is stronger compared to that of *Amnioquick rapid test*.

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Research Article

# Endometrial Histology in Abnormal Uterine Bleeding with Risk Factors

## *Gambaran Histologi Endometrium PUA dengan Faktor Risiko*

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## Abstract

**Objective:** To determine the endometrial histology in abnormal uterine bleeding (AUB) patients with risk factors.

**Method:** This study involved 30 patients with complaints of AUB, aged over 35 years with associated risk factors of parity, obesity and fasting blood glucose in the outpatient clinic at Prof. Dr. R. D. Kandou General Hospital Manado, from July 2013 until October 2013. Patients who agreed to be involved in this study, underwent dilatation and curettage (D&C) to assess the endometrial histology that was grouped as the hyperplasia and non-hyperplasia groups.

**Result:** From the results of the study, 7 patients were in the 35-40 years age group (23.3%) and in the 41-50 years age group were 23 patients (76.7%). Based on parity, 11 patients (36.7%) were nulliparous and 19 patients (63.3%) were multiparous. Based on the BMI, 16 patients (53.5%) were obese and 14 patients (46.7%) were non-obese. And based on the results of fasting blood sugar, similar results was obtained in normal and abnormal fasting blood glucose with the results of 15 patients in each groups (50%). And from all of patients who underwent D&C, endometrial hyperplasia was shown in 21 patients (70%) and non-hyperplasia endometrium in 9 patients (30%). From the results of Fischer exact test, a significantly high association was obtained between BMI and fasting blood glucose with the occurrence of endometrial hyperplasia.

**Conclusion:** There is a significant relationship between BMI and high fasting blood glucose with endometrial hyperplasia.

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**Keywords:** age, AUB, BMI, endometrial hyperplasia, fasting blood sugar, parity

## *Abstrak*

***Tujuan:*** *Untuk mengetahui gambaran histologi endometrium pada penderita PUA dengan faktor risiko.*

***Metode:*** *Penelitian ini melibatkan 30 pasien dengan keluhan PUA yang berusia di atas 35 tahun dan dihubungkan dengan faktor risiko paritas, obesitas dan gula darah puasa di poliklinik RSUP Prof. Dr. R. D. Kandou Manado, sejak Juli 2013 sampai Oktober 2013. Pasien yang telah setuju untuk terlibat dalam penelitian ini dilakukan D&C untuk mengetahui gambaran endometrium yang dikelompokkan dalam kelompok hiperplasia dan non-hiperplasia.*

***Hasil:*** *Dari hasil penelitian terhadap 30 pasien yang datang dengan keluhan PUA dan setuju dilakukan D&C didapatkan hasil pada kelompok usia 35-40 tahun sebanyak 7 pasien (23,3%) dan kelompok usia 41-50 tahun sebanyak 23 pasien (76,7%). Berdasarkan paritas didapat 11 pasien (36,7%) nullipara dan 19 pasien (63,3%) multipara. Berdasarkan BMI didapatkan 16 pasien (53,5%) dengan obesitas dan pasien non-obese sebanyak 14 pasien (46,7%). Dan berdasarkan hasil gula darah puasa didapatkan hasil yang sama pada gula darah puasa normal dan gula darah puasa yang tidak normal dengan hasil masing-masing 15 pasien (50%). Dari semua pasien yang dilakukan D&C didapatkan hasil hiperplasia endometrium sebanyak 21 pasien (70%) dan non-hiperplasia endometrium sebanyak 9 pasien (30%). Dari hasil uji statistik Fischer exact test didapatkan hubungan yang bermakna antara BMI dan gula darah puasa yang tinggi dengan terjadinya hiperplasia endometrium.*

***Kesimpulan:*** *Terdapat hubungan bermakna antara BMI dan gula darah puasa yang tinggi dengan hiperplasia endometrium.*

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***Kata kunci:*** *gula darah puasa, hiperplasia endometrium, IMT, paritas, PUA, usia*

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## INTRODUCTION

Abnormal uterine bleeding (AUB) consists of all menstrual abnormalities, both in the amount and duration. Clinical manifestations may include bleeding, prolongation of menstrual cycle or irregular cycle.[1,2] AUB is a disorder most commonly encountered in daily practice in gynecology and a part of the largest problems in women. It is often present with varied clinical picture and is considered a complicated problem.[3] Its incidence amounts to 19.1% of all clinical visits for gynecological cases. In addition, it was reported that approximately 25% of all gynecologic surgery is related to abnormal uterine bleeding.[4]

AUB affects women by causing a decrease in productivity. This is due to a disturbance in the menstrual cycle and the amount of blood lost that can lead to anemia if not treated in a comprehensive manner. Given the high number of women of reproductive age in the population in Indonesia, and

the higher life expectancy in premenopausal and menopausal patients compared to the past, the negative impact of AUB will unconsciously decrease the productivity of Indonesia in the medium and long term.

Abnormal uterine bleeding can occur at any age between menarche and menopause, more commonly in the early years after menarche and at the end of the ovarian cycle. At perimenarche age, the most likely cause is a disorder of blood clotting factors and psychological causes.[4] At puberty and after menarche, abnormal uterine bleeding is caused by impaired or delayed maturation in the hypothalamus, which interrupts the gonadotropin hormone releasing factor and gonadotropin hormone. In particular, in adult women of reproductive age and in premenopausal period with abnormal uterine bleeding, curettage is necessary to determine the presence or absence of endometrial abnormalities. Endometrial curettage is also a procedure that is effective in confirming any endometrial abnormalities.[5]

Schröder, in 1915, conducted a histopathological study on the uterus and ovaries at the same time, drawing the conclusion that a bleeding disorder called hemorrhagic metropathy happens due to the persistence of follicles which is not broken, so there is no ovulation and corpus luteum formation. As a result, endometrial hyperplasia occurred due to excessive and continuous estrogen stimulation. This explanation is still acceptable for most cases of AUB.[6]

Endometrial hyperplasia is a condition in which the endometrium grows excessively. These abnormalities are benign, but in some cases can progress toward uterine malignancies. The histologic features of endometrial hyperplasia are glandular proliferation with changes in the shape and size, as well as an increase of glandular and stromal ratio.[7,8] In general, endometrial hyperplasia is divided into 4 types, namely simple, complex, simple with atypia and complex endometrial hyperplasia with atypia. Simple and complex endometrial hyperplasia is distinguished by changes in the structure of the complexity and amount of stroma between the glands, regardless of the existence of atypic cells.[8]

The diagnosis of atypical hyperplasia is based on the description of a specific core, the core is large, round, have irregular nuclear membrane, and is often accompanied by stratification of 2-4 cells with loss of polarity associated with the basement membrane. Chromatin is dispersed and clustered along the nuclear membrane to form a vesicular picture. These vesicular nuclei are characteristic of atypic hyperplasia.[9] Aiza Saadia et al found that 40 percent of endometrial hyperplasia was identified from the results of endometrial curettage and that endometrial curettage had 100 percent specificity in the diagnosis of endometrial abnormalities and endometrial cancer.[5]

Treatment with progesterone is an ideal treatment for simple or complex endometrial hyperplasia without atypia. Considering that both simple and complex atypical endometrial hyperplasia has the potential towards malignancy, the best treatment is hysterectomy.[9]

Some women are at higher risk of endometrial hyperplasia and endometrial cancer. Furthermore, endometrial hyperplasia is a precursor of endometrial cancer.[10,11] Patients with endometrial hyperplasia usually present with abnormal bleeding, which can include menorrhagia, metrorrhagia, menometrorrhagia, or postmenopausal bleeding. We must be cautious of endometrial cancer for people aged over 35 years who present with bleeding.[10]

Endometrial hyperplasia often occurs in some women who are at high risk.[11,12] This includes patients aged over 35 years, preceded by missed period or amenorrhea, obesity (causing peripheral conversion of androgens to estrogen in fat tissue), patients with diabetes mellitus, nulliparous, long-term users of estrogen without progestin administration in postmenopausal cases, PCOS, and patients with ovarian tumors of granulose theca cell types.

Endometrial cancer is still not familiar for the public. The type of cancer that is popular among women is breast cancer, cervical cancer, or uterine cancer. Although the likelihood of mortality or death rate of patients is smaller than that of other cancers, endometrial cancer still carries its own risks.[13]

When viewed in descriptive epidemiology, in Indonesia there is no data on the number of cases of endometrial cancer. RSCM Jakarta found 72 new cases during the year 1993-2004 and found that 63.9% of patients were aged >50 years. The incidence of endometrial cancer is increasing in Indonesia, because the majority of people are living longer and the presence of more accurate reporting. Approximately 32,000 cases are estimated to occur each year resulting in 5900 deaths. One third of

women with postmenopausal bleeding have uterine cancer. The average age of patients with endometrial cancer was 61, and most patients are at least 55 years old.[13]

Since the cervical cancer death rate has decreased by more than 50% due to the progress in screening and early detection, the incidence of endometrial cancer is found to be second in gynecologic malignancies. The number of people diagnosed with endometrial cancer each year continues to rise.[14]

In this study, patients with AUB accompanied by risk factors of over 35 years of age, obesity, high blood sugar and nulliparity, had their endometrial histology examined to determine the possibility of endometrial hyperplasia occurrence, which is a precursor of endometrial cancer. Endometrial sampling can be performed by dilatation and curettage, hysteroscopy, and endometrial aspiration. Dilatation and curettage is still regarded as the most effective method because other than as a diagnostic tool, it can also simultaneously control bleeding in patients with AUB without abnormalities in the uterus or systemic abnormalities.[15,16] Histologic examination in this study is conducted by dilatation and curettage for diagnosis as well as therapy in patients with abnormal uterine bleeding.[17,18]

In Manado, there are no studies showing the incidence of AUB that leads to endometrial hyperplasia and endometrial hyperplasia predisposing factors. Therefore, we aim to examine endometrial histology in patients with AUB aged >35 years old (reproductive age, premenopausal and menopause), with suspected risk factors affecting the possibility of malignancy.

## METHODS

This research is a cross sectional study with analytic approach. The population is AUB patients aged over 35 years who came for treatment at the outpatient clinic of Prof. Dr. R. D. Kandou General Hospital, Manado during the period of July 2013 to October 2013. This is also associated with risk factors of age, parity, obesity and fasting blood glucose. Patients who have agreed to participate in this study underwent D&C to determine the histologic picture of endometrium, and are grouped into the hyperplasia and non-hyperplasia group. The data obtained is analyzed statistically by performing Fischer's exact test to assess the significance of a relationship of the specified risk factors in influencing AUB.

## RESULTS

On the characteristics of the patient sample by age, we obtained that in our patients AUB most commonly occurred in the 41-50 years age group, consisting of 23 samples (76.7%), and in the 35-40 years age group consisted of 7 samples (23.3%). Based on parity, we obtained that the multiparous group consisted of a total of 19 samples (63.3%) and the nulliparous group consisted of 11 samples (36.7%). Based on the BMI classification, AUB patients were more likely to be obese with 16 samples (53.3%) in the obese group, while in the non-obese group consisted of 14 samples (46.7%). From the fasting blood glucose, either group of normal and abnormal glucose profile each obtained 15 samples (50%). After performing D&C on the 30 samples, it was found that 21 samples (70%) had hyperplasia, and 9 samples (30%) had non-hyperplasia.

**Table 1.** Sample Characteristics Based on Age

| Age | D & C Result | |
|---|---|---|
| | Hyperplasia | Non-Hyperplasia |
| 35-40 | 5 | 2 |
| 41-50 | 16 | 7 |

In regards to age, we obtained that among patients who were 35-40 years of age, 5 were found to have hyperplasia and 2 were observed as non-hyperplasia. Among patients over 40 years old, the result was 16 with hyperplasia and non-hyperplasia was as many as 7. Analysis using Fischer exact test found that p=1.00, indicating that there is no significant relationship between age and the status of endometrial hyperplasia.

**Table 2.** Sample Characteristics Based on Parity

| Parity | D & C Result | |
|---|---|---|
| | Hyperplasia | Non-Hyperplasia |
| Nulliparous | 8 | 3 |
| Multiparous | 14 | 5 |

In regards to parity, we found that in the nulliparous group, 8 patients had endometrial hyperplasia and 3 did not have hyperplasia. In the multiparous group, as many as 14 showed hyperplasia and 5 did not have hyperplasia. The p-value based on Fischer exact test was 1.00, implicating that there is

no relationship between parity with endometrial hyperplasia as determined by D & C.

**Table 3.** Sample Characteristics Based on BMI

| BMI | D & C Result | |
|---|---|---|
| | Hyperplasia | Non-Hyperplasia |
| > 25 | 16 | 0 |
| < 25 | 5 | 9 |

In our sample, all the patients in the obese group had endometrial hyperplasia. Meanwhile, among patients whose BMI was lower than 25 kg/m$^2$, five had hyperplasia and nine did not have hyperplasia. The results of Fischer exact test showed that there is a significant association between BMI status endometrial hyperplasia (p=0.00).

**Table 4.** Sample Characteristics based on Fasting Blood Glucose

| Fasting Blood Glucose | D & C Result | |
|---|---|---|
| | Hyperplasia | Non-Hyperplasia |
| Normal | 8 | 7 |
| Abnormal | 14 | 1 |

From the patient characteristics based on fasting blood glucose, we found that in the group with normal fasting blood glucose, eight had endometrial hyperplasia and seven did not. However, in patients with abnormal fasting blood glucose, as much as 14 patients had hyperplasia and only one was found without hyperplasia. The result of Fischer exact test indicates that there is a significant relationship between fasting blood glucose and endometrial hyperplasia (p=0.035).

## DISCUSSION

Based on our results, most of our patients were aged 41-50 years old (76.7%). Two-thirds of women who were treated for AUB in our hospital were aged over 40. In the study by Dinic et al in Serbia, it was concluded that the incidence of AUB increases with the age of patients. In their study, 2.13% was <30 years old, as much as 35.8% were aged 30-45 years old, and the majority was older than 45 years old (61.9%). The data characteristic above is similar to our study, in which patients with AUB mostly belonged to the 41-50 years age group.

After further analysis, we found that of the 23 samples aged 41-50 year old, 16 samples (69.5%) had endometrial hyperplasia and 7 samples did not have hyperplasia. Subhankar et al in India obtained as much as 34.5% endometrial hyperplasia with a sample of 252 patients and the highest incidence being in the perimenopausal age group (aged 46-50 years).[19]

In this study we found no association between age and status of endometrial hyperplasia, although there seems to be clinically significant endometrial hyperplasia occurring in above 40 years of age, with a total 16 of 23 samples. Statistically, this could be caused by a random error factor. In general, of all the subjects aged over 35 years old in this study, histology of hyperplasia was obtained in 21 patients.

Based on the characteristics of parity, we obtained that the patients with AUB in this study is mostly comprised of multiparous women (63.3%) and 36.7% consist of nulliparous women. These results is same with the results of Subhankar et al, that found 88.5% of 252 patients with AUB were multiparous.[19]

Out of the 11 patients who were nulliparous, 72.7% had a picture of endometrial hyperplasia, while out of the 19 multiparous patients as many as 14 patients (73.7%) had a picture of hyperplasia. Clinically, the incidence of endometrial hyperplasia is similar between nullipara and multipara, but statistically there was no significant association between parity and the status of endometrial hyperplasia. Theoretically, hyperplasia occurs more frequently in the nulliparous group, where there is an increase in cumulative exposure to estrogen because of the higher total number of menstrual cycles throughout life. Our results could be explained by the possibility of random error, and further research of AUB on nullipara population should be carried out.

Based on the characteristics of BMI we discovered that AUB incidence was slightly higher in the obese group (53.3%), compared to the non-obese group (46.7%). Parazzini et al in Italy observed that 60.4% of endometrial hyperplasia patients had BMI >25. Of the 16 samples with obesity, all of them had the histologic picture of endometrial hyperplasia, so that clinical data shows the influence of obesity on endometrial hyperplasia. Whereas the sample with a lower BMI, showed that the majority did not have endometrial hyperplasia. Statistical tests showed that there was a significant relationship

between BMI with endometrial hyperplasia. So both clinically and statistically, our result was in accordance with the theory in which hyperplasia is a disease that is estrogen-dependent, with endogenous and exogenous estrogen stimulating endometrial proliferation excessively.[12]

Based on the fasting blood glucose, the normal and abnormal groups both had equal samples. In statistical tests, we obtained that in the group with abnormal fasting blood glucose the results is not normal, with 14 samples showing histologic picture of endometrial hyperplasia. Meanwhile, the occurrence of endometrial hyperplasia is approximately equal in populations with normal blood sugar. Clinically, we obtained that 93.3% of samples with high fasting blood glucose had symptoms of AUB showing histology of endometrial hyperplasia. Statistically, we found a significant relationship between fasting blood glucose and endometrial hyperplasia. This is consistent with the theory stating that women with diabetes have a two-fold risk of developing endometrial hyperplasia.[20] Lindemann et al (2010) mentioned that the risk of developing endometrial cancer is three times higher in diabetes patients.[11]

## CONCLUSION

There is a significant relationship between BMI and high fasting blood glucose with endometrial hyperplasia, but this significant relationship was not identified between age and parity towards endometrial hyperplasia. This research is a beginning to reveal the endometrial histology in AUB, in relation with numerous risk factors. In this study, we hypothesized that examination of BMI and fasting blood glucose can be used to predict the likelihood of malignancy in patients with AUB. However, further research is needed with a larger sample size and evaluating other risk factors to improve the accuracy of the study.

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Research Article

# Pentoxifylline as a Therapy for Thin Endometrial Lining in Infertility

## *Pentoksifilin sebagai Terapi Endometrium Tipis pada Infertilitas*

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## Abstract

**Objective:** To evaluate the effect of pentoxifylline as a single regimen therapy for thin endometrial lining in infertility.

**Method:** A cross-sectional retrospective research was held in Yasmin Clinic - Kencana, Dr. Cipto Mangunkusumo Hospital from 2010 until 2011. Our respondents were women with infertility problem.

**Result:** There was significant improvement of endometrial lining in respondents who received pentoxifylline in the first month ($p<0.0001$).

**Conclusion:** There was significant improvement of endometrial lining after pentoxifylline therapy.

[Indones J Obstet Gynecol 2015; 3: 151-153]

**Keywords:** infertility, pentoxifylline, thin endometrium

## *Abstrak*

***Tujuan:*** *Menilai efek pentoksifilin sebagai terapi tunggal untuk dinding endometrium tipis pada masalah infertilitas.*

***Metode:*** *Penelitian potong-lintang retrospektif dilakukan di Klinik Yasmin - RSCM Kencana sejak 2010 sampai 2011. Responden merupakan perempuan dengan permasalahan infertilitas.*

***Hasil:*** *Terdapat peningkatan tebal endometrium pada responden yang mendapat pentoksifilin pada bulan pertama ($p<0,0001$).*

***Kesimpulan:*** *Terdapat perbaikan bermakna pada dinding endometrium setelah terapi pentoksifilin.*

*[Maj Obstet Ginekol Indones 2015; 3: 151-153]*

***Kata kunci:*** *endometrium tipis, infertilitas, pentoksifilin*

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## INTRODUCTION

Success rate of in vitro fertilization depends on two main things, namely the quality of the embryo and the atmosphere of endometrium during implantation. Endometrium has two phases during each menstrual cycle, which are proliferative and secretion phase.[1] Physiologic changes in endometrial lining consists of increased functional layer thickness and increased spiral artery to prepare for implantation. If those changes fail to achieve pregnancy, menses occur.[2,3] Therefore, to facilitate a successful pregnancy, an adequate growth of endometrium is necessary.[3,4]

Several literatures stated the presence of a significant relation between endometrial thickness with pentoxifylline (PTX) therapy, however some failed to show the effect. The thickness of endometrial lining will improve the success rate of pregnancy in assisted reproductive technology (ART).[1,5]

PTX is a phosphodiesterase inhibitor derived from methylxanthine, a vasodilating chemical substance which can induce morphologic changes in erythrocytes, prevent inflammation process, and reduce blood viscosity by preventing platelet aggregation process and increasing concentration of intracellular cyclic nucleotide.[6-9] Currently, PTX is used as therapy for vascular problems, such as intermittent claudication, ischemic ulcers and many more.[8]

This research was performed to evaluate the significance of improvement in endometrial lining with PTX as a single regimen therapy. In many developed countries, PTX has entered clinical trials with placebo, providing a variety of results. Nowadays, ART is beginning to develop in Indonesia, thus it is considered important to perform a direct evaluation of PTX.

## METHODS

This study was carried out in cross sectional design involving 22 respondents, and took place in Yasmin Clinic Kencana, Dr. Cipto Mangunkusumo Hospital from 2010 to 2011. Target population for this study was patients presenting for infertility problems to Yasmin Clinic and fulfilled the inclusion criteria. Inclusion criteria for our study were women who agreed to join the study, patients with infertility, and patients with endometrial thickness <6 mm; while our exclusion criteria were those who had pelvic inflammatory disease. We defined thin endometrium as a condition where the functional layer of endometrium during the secretory phase is less than 6 mm in thickness, while no hormonal imbalance or infections were identified from our examinations.

Endometrial thickness was assessed using transvaginal ultrasound at mid-luteal phase by a single operator. The assessment was performed at baseline before PTX therapy administration, then the patient's endometrial thickness was reassessed in the second and third month after receiving PTX continuously.

## RESULT

Of the twenty-two samples collected, we found that the patients' age ranged from 29 to 44 years, with a median of 36 years old. Most of the samples (9.41%) had unexplained infertility, whereas we also identified other causes such as endometrial polyps (1.5%), IVF failure (1.4%), and polycystic ovaries (1.5%).

**Table 1.** Age Characteristic Description

| Patient age characteristic (n = 22) | age (year) |
|---|---|
| Median | 36 |
| Minimum | 29 |
| Maximum | 44 |

The endometrial thickness in the first month before administration of PTX ranged between 2.8-5 mm with a median value of 5 mm; while in the second month, the range is increased to 4-14 mm with a median value of 7.0 mm; and in the third month ranged between 4-12 mm with a median value of 8.0 mm. According to statistical calculations with repeated measure method (Friedman), we obtained a p-value of <0.0001, which shows the significance between endometrial thickness before and after PTX therapy. The study shows that endometrial thickness increased in 18 respondents (82%) in the second month, and continued to increase in 9 respondents (41%) in the third month, while 1 respondent experienced decrease in thickness. For endometrial thickness in the second month compared to the previous month in which the patient has not received PTX treatment, we obtained a p-value <0.0001; and for the third month to the second month, we obtained p-value <0.0001.

In the first month of PTX therapy, 18 respondents (82%) experienced an increase in endometrial thickness and four respondents (18%) showed no change in endometrial thickness. Meanwhile, in the second to third months, nine respondents (41%) showed improvement of endometrial lining, 12 respondents had no change, and one respondent (5%) actually had declining endometrial thickness.

**Table 3.** Endometrial Thickness Change in the First, Second and Third Month

| | 1st and 2nd month n(%) | 2nd and 3rd month n(%) |
|---|---|---|
| Increase | 18 (82) | 9 (41) |
| No change | 4 (18) | 12 (54%) |
| Decrease | 0 (0) | 1 (5%) |

We encountered adverse effect in three patients, with nausea and dizziness at the first week after using pentoxyphiline. After receiving education and observation, after two weeks the symptoms disappeared.

**Table 2.** Endometrial Thickness in the First Month of Therapy (not yet receiving PTX), Second and Third Month (after receiving PTX)

| | 1st month | 2nd month | 3rd month | p-value |
|---|---|---|---|---|
| Endometrial thickness (mm) (median[min-max]) | 5 (2.8 - 5) | 7 (4 - 14) | 8 (4 - 12) | <0.0001 |

## DISCUSSION

The results obtained from our study, demonstrate the significance of the relationship between endometrial thickness before and after PTX therapy. This can be explained because PTX supplementation may increase cAMP function and decrease levels of TNF-α which may improve the process of implantation. Administration of PTX also results in increased flexibility and decreased erythrocyte aggregation of platelets, thereby increasing blood flow to the small capillaries in the endometrium, the result of which can be assessed from the thickness of the endometrium.

PTX as a therapy regimen may provide potential improvements affecting microvascularization, thus repairing thin endometrium and also improving tissue oxygenation.

## CONCLUSION

PTX therapy significantly increases endometrial thickness in patients with thin endometrium. PTX can be used to improve the thickness of the endometrium in these patients.

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Research Article

# IIIB-IV Degree Perineal Rupture Repair Using Overlapping and End-to-End Techniques with Pudendal Block Anesthesia

## *Hasil Reparasi Robekan Perineum Derajat IIIB-IV Teknik Tumpang Tindih dan Ujung ke Ujung dengan Anestesi Blok Pudendal*

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## Abstract

**Objective:** To compare the incidence of persistent sonographic anal sphincter defect, fecal urgency, anal and fecal incontinence after IIIb-IV degree perineal rupture repair using overlapping and end-to-end technique.

**Method:** An open clinical trial with randomization was carried out in July 2010-April 2012. The population consisted of the patients who underwent vaginal delivery in Dr. Sardjito Central General Hospital, Sleman District General Hospital, as well as Tegalrejo, Jetis and Mergangsan Community Health Centers who did no have complaints of fecal urgency, anal incontinence, and/or fecal incontinence, and suffered IIIb-IV degree perineal rupture repaired within less than 24 hours of rupture. The exclusion criteria included conditions in which patients could not undergo repair at the moment (shock, uncooperative patient). Fourty-eight research samples were divided into 2 groups, 24 samples for each of the treatment group (overlapping repair) and the control group (end-to-end repair). Local anesthesia was performed in a pudendal-block manner.

**Result:** Success of the repair was assessed based on the presence of persistent sonographic anal sphincter defects in the 6-week evaluation after repair. Successful repair was higher in the overlapping group than that of the end-to-end group (94.74% vs 81.25%, p=0.31). Clinically and based on the Fecal Continence Scoring Scale (FCSS), evaluation at weeks II and VI indicated successful repair in both groups.

**Conclusion:** There was no difference in the incidence of persistent sonographic anal sphincter defects, fecal urgency, anal incontinence, and fecal incontinence, after IIIb-IV degree perineal rupture repair using overlapping technique in comparison with end-to-end technique.

[Indones J Obstet Gynecol 2015; 3: 154-160]

**Keywords:** end-to-end technique, III-IV degree perineal rupture, obstetric perineal rupture, overlapping technique

## *Abstrak*

***Tujuan:*** *Untuk membandingkan kejadian persistent sonographic anal sphincter defect, urgensi fekal, inkontinensia anal maupun fekal, pascareparasi robekan perineum derajat IIIb-IV dengan teknik tumpang tindih dan ujung ke ujung.*

***Metode:*** *Dilakukan penelitian uji klinis terbuka dengan randomisasi pada bulan Juli 2010-April 2012. Kriteria inklusi adalah pasien persalinan pervaginam di RSUP Dr. Sardjito, RSUD Kabupaten Sleman, Puskesmas Tegalrejo, Jetis dan Mergangsan, Yogyakarta, yang sebelumnya tidak memiliki keluhan urgensi fekal, inkontinensia anal, dan/atau inkontinensia fekal, yang mengalami robekan perineum derajat IIIb-IV dengan reparasi kurang dari 24 jam sejak kejadian ruptur. Kriteria eksklusi adalah pasien yang tidak memungkinkan untuk dilakukan reparasi saat itu (syok, tidak dapat bekerja sama). Empat puluh delapan sampel penelitian dibagi dalam dua kelompok, masing-masing 24 sampel pada kelompok perlakuan (reparasi tumpang tindih) dan kelompok kontrol (reparasi ujung ke ujung). Anestesi lokal dilakukan secara blok pudendal.*

***Hasil:*** *Keberhasilan reparasi dinilai dari gambaran persistent sonographic anal sphincter defect 6 minggu pascareparasi. Keberhasilan pada kelompok tumpang tindih lebih tinggi dibandingkan kelompok ujung ke ujung (94,74% vs 81,25%, p=0,31). Secara klinis maupun berdasarkan FCSS (Fecal Continence Scoring Scale), evaluasi minggu kedua dan keenam menunjukkan keberhasilan reparasi di kedua kelompok.*

***Kesimpulan:*** *Tidak terdapat perbedaan kejadian persistent sonographic anal sphincter defect, urgensi fekal, inkontinensia anal maupun fekal pascareparasi robekan perineum derajat IIIb-IV dengan teknik tumpang tindih dan teknik ujung ke ujung.*

*[Maj Obstet Ginekol Indones 2015; 3: 154-160]*

***Kata kunci:*** *robekan perineum obstetri, robekan perineum derajat III-IV, teknik tumpang tindih, teknik ujung ke ujung*

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## INTRODUCTION

Vaginal deliveries remain regarded as the most secure and economical delivery procedures.[1] In well-conducted aid measures for vaginal delivery, more than 85% of women experience perineal trauma, and about 60-70% of them require repair. Some patients

even experience III-to-IV degree perineal rupture. Research in Europe shows that as many as 0.5-3% of III-IV degree perineal rupture can be encountered, while in the United States the incidence reach 6-9%, with some sources reporting it to be 20%.[2-5] The incidence varies due to differences in the system used to measure the rupture degree, ignorance of both delivery helpers and delivery patients, as well as the assumption that perineal trauma and its accompanying problems are something normal as a consequence of vaginal deliveries.[6]

The standard technique for III-IV degree perineal rupture repair is external anal sphincter suturing using an end-to-end technique. In 1999, Sultan et al introduced a new technique, namely an overlapping technique, and reported a decrease in the incidence of anal incontinence from 41% to around 8% in patients undergoing an overlapping repair technique. Research by Fernando et al noted the incidence of fecal urgency to be 32% in end-to-end cases and 3.7% in overlapping cases (p=0,02).[7]

Perineum is the outer door of the pelvis that is divided into 2 triangles. The front triangle is called the urogenital triangle, and the triangle located behind the end of the anal canal is the anal triangle. The anal sphincter complex spans 3-4 cm in length and consists of external and internal anal sphincters. 'Loop concepts' (upper, middle, and basal loops) feature a single sphincter unit, which have different structures and functions.[8-11] The perineal body is a three-dimensional central point between the urogenital triangle and the anal triangle, consisting of the bulbospongiosus muscle fibers, superficial transverse perineal muscle fibers and external anal sphincter muscles.[8,11-13]

Several risk factors for perineal rupture include prolonged second stage, precipitated parturition, a history of perineal rupture, large babies, malposition, instrument-assisted delivery, short perineum, and episiotomy, as well as infiltration of local anesthetics.[1,3,12,14-17] There are two types perineal rupture due to obstetric anal sphincter injuries, overt and occult. The latter type usually occurs as a result of the error determining the diagnosis, when the III-IV degree perineal rupture is considered to be II degree.[18]

According to Sultan, there are classifications for perineal trauma, namely grade I, which comprise only the vaginal epithelium or perineal skin lacerations; grade II, when only involving the perineal muscles; grade III, which is rupture that reaches the anal sphincter, which is further divided into IIIa (<50% of the external anal sphincter), IIIb (>50% of the thickness of the external anal sphincter), and IIIc (when the rupture reaches the internal anal sphincter); and grade IV, which is the III-degree rupture accompanied with anal mucosa.[3,7,16,19,20]

Obstetricians have recognized the end-to-end technique since a long time ago as traditional/standard techniques. The overlapping technique is more widely used by colorectal surgeons and in gynecology in cases of fecal incontinence. In general, the results of the repair depend highly on the diagnostic accuracy, the selected repair technique, the thread used, as well as post-repair treatment. Local anesthesia (infiltration or pudendal block) can be used on almost all measures of perineal repair, although general or regional anesthesia produces better sphincter relaxation.[3,7,9,21-23] Evaluation on results of repair is performed at weeks 1, 2, 6, and 3 months after repair. Complaints to be evaluated are complaints related to suturing, possibility of infection up to dehiscence, impaired urination, defecation and dyspareunia.[5] Evaluation in the third month can be done using ultrasonography, anal manometry, electromyography, measurement of pudendal nerve terminal latency time, and magnetic resonance imaging (MRI).[21,24-27]

Pudendal nerves are somatic nerves found in the pelvic region that innervate the external genitalia in both men and women. These nerves originate from the sacral plexus, from the S2 to S4 ventral rami. The pudendal block anesthesia provides local anesthesia to the perineal region and to approximately the lower third of the vagina. Complications include allergic reactions, systemic toxic reactions, vaginal wall lacerations, hematoma, infections and subgluteal abscess, until fatal complications (convulsions to death).[11,23,28-30] The anesthetic drug of lignocaine 1-2% either with or without adrenaline is diluted into 0.5%. The maximum dose is 4 mg/kg body weight for lignocaine without adrenaline, and 7 mg/kg weight for lignocaine with adrenaline (1:200.000).[31] The pudendal-block anesthetic technique is a relatively inexpensive anesthetic technique, is quite easy to perform and can be done in all delivery-assisting places.

In this study, we aim to compare the incidence of persistent sonographic anal sphincter defect, fecal urgency, anal and fecal incontinence after IIIb-IV degree perineal rupture repair using overlapping and end-to-end technique.

## METHODS

This study was an open clinical trial with computer randomization. Patients were divided into two groups, the treatment group receiving overlapping perineal rupture repair, and the control group receiving end-to-end repair.

The population consisted of patients who underwent vaginal delivery with perineal rupture degrees IIIb, IIIc or IV, hospitalized in Dr. Sardjito Central General Hospital, Sleman District General Hospitals, as well as Tegalrejo, Jetis and Mergangsan Community Health Centers in Yogyakarta. The inclusion criteria included patients without previous complaints of fecal urgency, fecal or anal incontinence, with the repair being performed within less than 24 hours of the rupture, and the patients were willing to participate in the study. The exclusion criteria included conditions where the patients could not undergo repair at the moment (shock or uncooperative patient). The study was conducted from July 2010 until April 2012.

The independent variable consisted of perineal rupture degrees IIIb, IIIc or IV repair using overlapping and end-to-end techniques. The dependent variable was repair success defined as the absence of persistent sonographic anal sphincter defects, fecal urgency, anal incontinence, and fecal incontinence.

Repair was initiated with pudendal-block anesthesia using lidocaine 1%.[23,30] The rectal mucosa was sutured using interrupted sutures with polyglactin 910 thread number 3-0, intraluminal knots, followed by continued suturing of internal anal sphincter. Repair of the external anal sphincter was performed using techniques determined based on computer randomization, including the overlapping technique and end-to-end technique, with polyglactin 910 thread number 2-0. The end-to-end repair technique is a suturing technique performed by bringing the ends of the external anal sphincter on both sides to be united and to perform sutures at the ends of the muscles with sufficient thickness (3-4 sutures). The overlapping repair technique is a suturing technique that brings together the ends of the external anal sphincter with mattress sutures resulting in a greater surface of inter-contacting tissues between the two ends of the muscles.[9] Perineal muscles were sutured interruptedly using the same thread. Repair of the vaginal mucosa began at 1 cm above the top of the rupture wounds, with unlocked running sutures, and then the perineal skin was sutured using continuous subcuticular suturing, using polyglactin 910 number 3-0.

Persistent sonographic anal sphincter defects refer to fixed pictures of ultrasonography in the forms of anal sphincter muscle defects after perineal rupture repair, either with or without clinical complaints.[25,26] Fecal urgency refers to the condition where patients feel like they would like to have a bowel movement and cannot hold it until they arrive at the toilet (less than 5 minutes).[3,32] In this study, anal incontinence is used in cases of flatus incontinence in order to distinguish it from fecal incontinence, which is defined as the inability to control the discharge of liquid and solid feces.[16,17,32]

Antibiotics were given prior to the repair action, that was 1 gram of Ampicillin intravenously, with allergy testing performed beforehand. Patients with allergies can take 1 gram of Cefotaxime. Oral antibiotic Ampicillin caplets 500 mg/6 hours and Metronidazole tablets 500 mg/8 hours were given for 5 days. Analgesics were given orally, specifically mefenamic acid caplets 500 mg every 8 hours, or ibuprofen tablets 100 mg every 12 hours for 5 days. A spoon of laxantia syrup was given every 12 hours for 7 days along with a high-fiber diet. Suppository drug administration was not allowed.

The Dauer catheter number 14F was installed for 24 hours. Residual urine examination was performed no later than 6 hours after the catheter had been removed and the patient could urinate spontaneously. Perineal treatment was done by always maintaining cleanliness. The patient could be discharged from the hospital after they could urinate spontaneously without any complaint.

Evaluation at weeks 1 and 2 after the repair was made to assess any complaints, the condition of the repaired tissue, the ability of flatus and bowel movement. Assessment was also carried out to fill the Fecal Continence Scoring Scale.[3] At week 6, evaluation was performed using digital rectal examination and ultrasonography. Pelvic floor muscle exercises in a Kegel manner was introduced to patients at week 1 after repair.

Ultrasonography examination using a Voluson 730 pro 3D USG tool in a transperineal manner was performed to assess the presence of persistent sonographic anal sphincter defects. Abdominal probe that had been lubricated and covered with a special type of plastic was placed on the fourchette. Assessment was made to determine the presence or absence of defects in the internal and external anal sphincter.

Repair was considered successful if there were no persistent sonographic anal sphincter defect pictures obtained in the evaluation at week 6 after repair. Repair was considered as failed if there were pictures of persistent sonographic anal sphincter defects, and/or fecal urgency complaints, and/or anal incontinence, and/or fecal incontinence obtained at week 6 after repair, when dehiscence until the external anal sphincter occurred, or when failure or complications of anesthesia occurred.

## RESULTS

Forty-eight research samples with IIIb-IV degree perineal rupture were recruited, 24 patients randomized to the repair group using an overlapping technique and 24 patients randomized to the repair group using an end-to-end technique.

During the week 1 and 2 evaluation, all the patients were considered to have successful repair of the perineal rupture. After 6 week evaluation, there were 5 patients who cannot be contacted in the overlapping group, while in the end-to-end group there were 8 patients who cannot be contacted for follow-up. Therefore, we have 19 samples in the overlapping group and 16 samples in the end-to-end group at 6 weeks post-repair. There was one sample who had failed repair in the overlapping group, while three patients in the end-to-end group had failed repair.

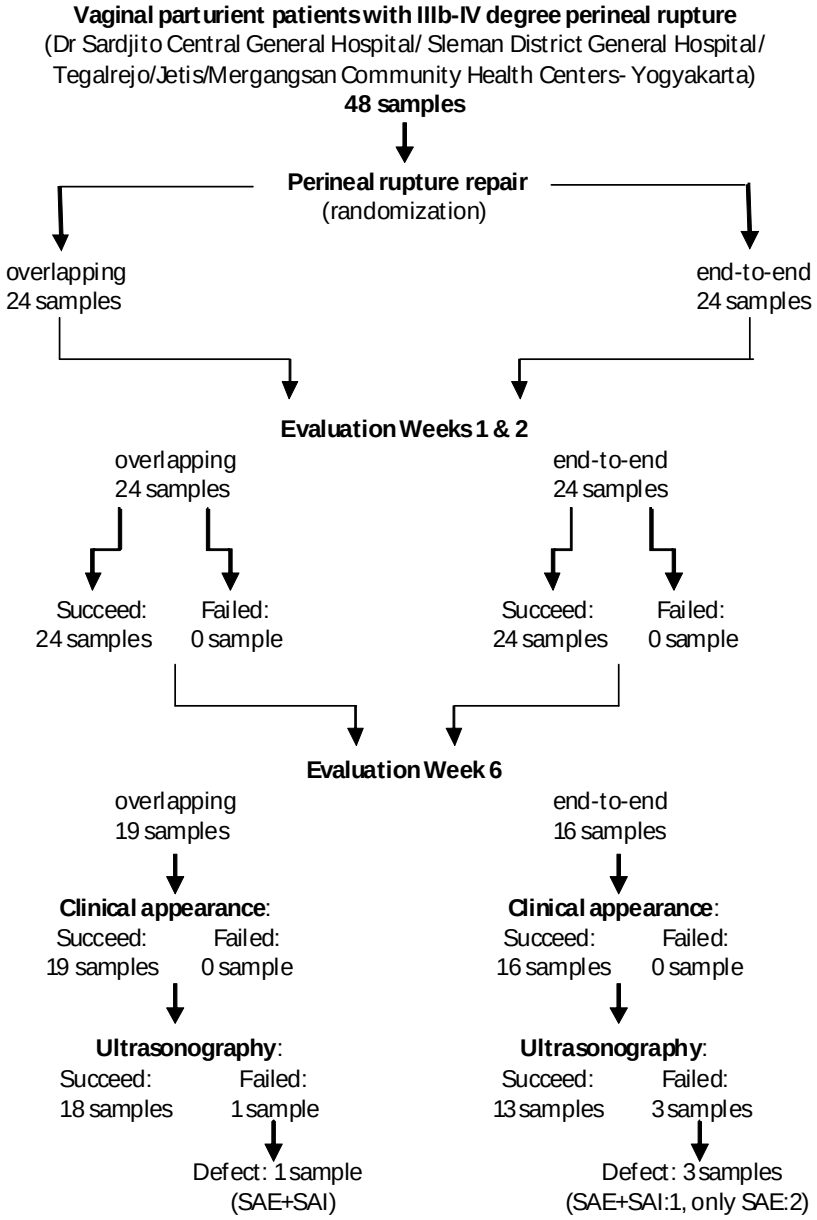

**Table 1.** The Occurrence of Persistent Sonographic Anal Sphincter Defects at Evaluation Week 6

| Repair Technique | Internal anal sphincter defects | | % | RR (95%CI) | p |
|---|---|---|---|---|---|
| | Yes | No | | | |
| Overlapping | 1 | 18 | 5.26 | 0.83 (0.05-14.48) | 1.00 |
| End-to-End | 1 | 15 | 6.25 | | |
| **Repair Technique** | **External anal sphincter defects** | | **%** | **RR (95%CI)** | **p** |
| | **Yes** | **No** | | | |
| Overlapping | 1 | 18 | 5.26 | 0.24 (0.02-2.58) | 0.24 |
| End-to-End | 3 | 13 | 18.75 | | |

We can see from Table 1 that in the group who underwent overlapping repair, the sample who had persistent sonographic anal sphincter defect had internal and external anal sphincter defect. Out of the three samples who had failed repair, one sample had internal and external anal sphincter defect, and the other two patients only suffered external anal sphincter defect. However, this difference was not found to be significant statistically.

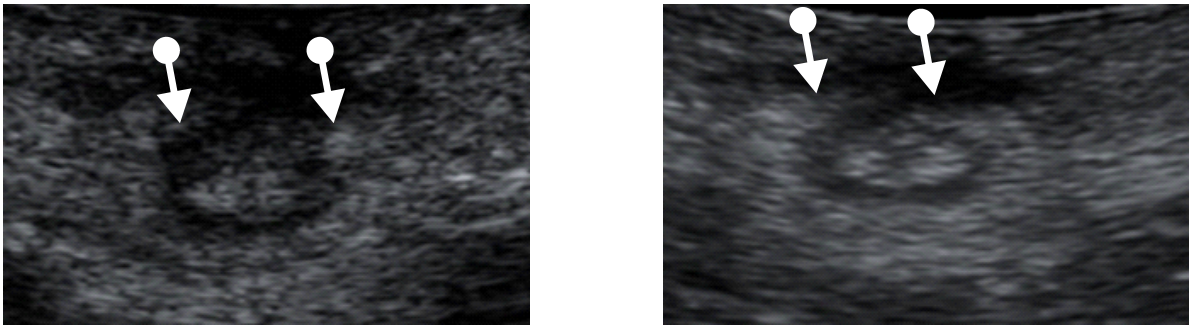

**Figure 1.** Ultrasonography Pictures for Sample Number 29

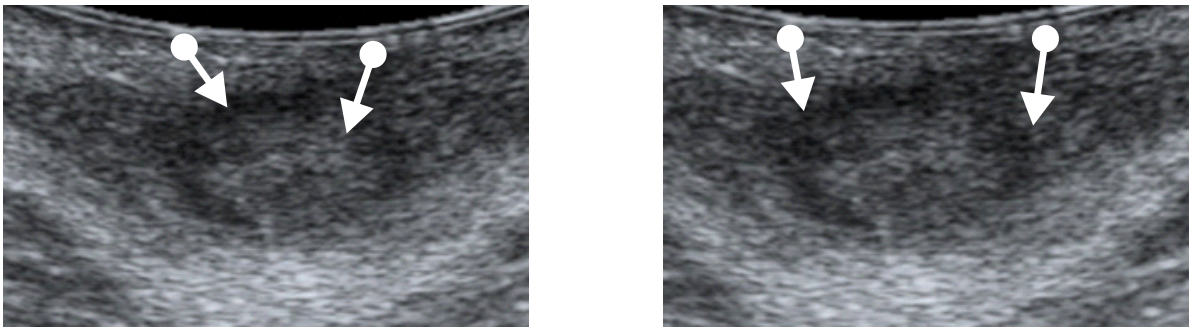

**Figure 2.** Ultrasonography Pictures for Sample Number 44

**Table 2.** Success of Perineal Repair (Ultrasonography) at Evaluation Week 6

| Repair Technique | Repair Success | | % | RR (95%CI) | p |
|---|---|---|---|---|---|
| | Yes | No | | | |
| Overlapping | 18 | 1 | 94.74 | 4.15 (0.39-44.57) | 0.31 |
| End-to-End | 13 | 3 | 81.25 | | |

**Table 3.** Success of Perineal Repair (Clinical) in Evaluation Weeks 2 and 6

| Repair Technique | Repair Success at Week 2 | | | Repair Success at Week 6 | | |
|---|---|---|---|---|---|---|
| | Yes | No | % | Yes | No | % |
| Overlapping | 24 | 0 | 100 | 19 | 0 | 100 |
| End-to-End | 24 | 0 | 100 | 10 | 0 | 100 |

From Table 2 we can see that the success rates of both repair techniques were high, with the overlapping technique having 94.74% success rate, and the end-to-end technique had 81.25% success rate. Statistically, no significant difference was found between both groups (p=0.31). However, from Table 3 we can see that no clinical indication of failed repair was found in either groups at both the 2-week and 6-week evaluation.

## DISCUSSION

The research findings show that the samples in both groups are homogeneous. The success of repair was assessed based on the presence or absence of images related to persistent sonographic anal sphincter defect in the 6th week evaluation after repair. In this assessment, successful repair in the overlapping group reached 94.74%, higher than the end-to-end group (81.25%). However, it was not found to be significantly different (p=0.31). Some risk factors were jointly present in 3 out of the 4 samples who had failed repairs. However, no variable was found to be more influential than the others in the incidence of persistent sonographic anal sphincter defects.

Clinically and based on the FCSS, evaluation after repair at weeks 2 and 6 indicated successful repair of both groups. There were 3 out of 4 samples with anal sphincter defects, which experienced dehiscence up to the subcutaneous area (one of them even presented with pus), in the evaluation at week 1 after repair. This dehiscence did not reach the external anal sphincter. The treatment given resulted in tissue repair at the 2nd week evaluation.

At the 6th week evaluation after repair, the sample size had been reduced by 13 subjects. This was due to the inability to contact the samples for follow-up until week 12 after the repair. The reason most commonly found for this situation was the return of the samples to their hometown after the completion of their puerperium and the eruption of Mount Merapi in Yogyakarta, especially in the area of Sleman Regency.

Based on the data presented, it remains necessary to conduct further research in Indonesia with more samples in order to generate maximum research findings. The selection of either overlapping or end-to-end repair technique should be adapted to the perineal conditions and situations at the time the repair is performed since the success rates of both techniques did not show a significant difference.

## CONCLUSION

In this study, there were no differences in the incidence of persistent sonographic anal sphincter defects after IIIb-IV degree perineal rupture repair using an overlapping technique in comparison with an end-to-end technique. Similarly, there were no differences in terms of repair results in relation to the presence of fecal urgency, anal incontinence, and fecal incontinence.

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Research Article

# Accuracy of Intraoperative Frozen Section in Diagnosing Malignancy of Ovarian Neoplasm

## *Akurasi Pemeriksaan Potong Beku Intra-Operatif dalam Mendiagnosa Keganasan Neoplasma Ovarium*

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## Abstract

**Objective:** To evaluate the accuracy of frozen section for ovarian neoplasm in our hospital.

**Method:** A retrospective evaluation was conducted on medical records of patients with ovarian neoplasms who underwent a frozen section laparotomy between the years 2008 and 2013 at Dr. Cipto Mangunkusumo Hospital. Records with incomplete data on frozen section or paraffin block report were excluded. Criteria for frozen section laparotomy in our facility was based on a malignancy score of equal to or more than 6. Frozen section reports were compared to paraffin block report based on benign, borderline, or malignant cases.

**Result:** From 139 patients with ovarian neoplasm, only 91 patients fulfilled the inclusion and exclusion criteria. Frozen section examination revealed benign cases was 15.4%, borderline cases was 15.4%, and malignant cases was 69.2%. Based on histopathological type, clear cell cystoadenocarcinoma was the most commonly observed histotype (19.8%). The sensitivity of frozen section for benign, borderline, and malignancy cases respectively was 81.8%, 76.9%, 91.0%. The specificity of frozen section for benign, borderline, and malignancy case respectively was 93.8%, 94.8%, 91.6%.

**Conclusion:** We found that the accuracy of intraoperative frozen section in our facility is adequate to diagnose ovarian neoplasm and can be used to assist in determining the extent of surgical management.

[Indones J Obstet Gynecol 2015; 3: 161-164]

**Keywords:** frozen section, ovarian neoplasm, paraffin block, sensitivity, specitificity

## *Abstrak*

***Tujuan:*** *Mengetahui akurasi pemeriksaan potong beku pada kasus tumor ovarium di rumah sakit kami.*

***Metode:*** *Penelitian ini menggunakan desain retrospektif berdasarkan rekam medis pasien dengan tumor ovarium yang dilakukan prosedur laparotomi dengan pemeriksaan potong beku pada tahun 2008-2013 di Rumah Sakit Dr. Cipto Mangunkusumo. Rekam medis dengan laporan potong beku atau blok paraffin yang tidak lengkap dieksklusi dari penelitian. Kriteria untuk dilakukan potong beku pada pasien di rumah sakit kami menggunakan skor keganasan sama atau lebih dari 6. Laporan pemeriksaan potong beku dibandingkan dengan pemeriksaan blok paraffin dengan kesimpulan kasus jinak, borderline, atau ganas.*

***Hasil:*** *Dari 139 pasien dengan tumor ovarium, hanya 91 pasien yang memenuhi kriteria inklusi dan eksklusi. Berdasarkan laporan potong beku didapatkan 15,4% kasus jinak, 15,4% kasus borderline, dan 69,8% kasus ganas. Sensitivitas dari potong beku untuk kasus jinak, borderline, dan ganas secara berturut-turut adalah 81,8%, 76,9%, 91,0%. Spesifisitas dari potong beku untuk kasus jinak, borderline, dan ganas secara berturut-turut adalah 93,8%, 94,8%, 91,6%.*

***Kesimpulan:*** *Akurasi dari pemeriksaan potong beku intra-operasi di rumah sakit kami cukup baik untuk mendiagnosa keganasan ovarium dan dapat digunakan sebagai pertimbangan mengambil keputusan dalam manajemen selanjutnya.*

*[Maj Obstet Ginekol Indones 2015; 3: 161-164]*

***Kata kunci:*** *blok paraffin, potong beku, sensitivitas, spesifisitas, tumor ovarium*

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## INTRODUCTION

Ovarian cancer represents the fifth most commonly diagnosed cancer among women in the world, and causes more deaths per year than any other female gynecologic malignancy.[1,2] There are three forms of epithelial ovarian neoplasm, namely benign, borderline, and malignant.[3] Based on histological type, type I is composed of low-grade serous, low-grade endometrioid, clear cell, mucinous and transitional (Brenner) carcinomas. These tumors generally behave in an indolent fashion, are confined to the ovary at presentation and, as a group, are relatively genetically stable. Another group of tumors, type II include conventional high-grade serous carcinoma, undifferentiated carcinoma, and malignant

mixed mesodermal tumors (carcinosarcoma) and this tumor is highly aggressive, evolves rapidly and almost always presents in advanced stage.[4,5]

Preoperative discrimination of adnexal mass can be made with Risk of Malignancy Index (RMI) or using a malignancy score in our center.[6-8] Intraoperative diagnosis is conducted through frozen section by evaluating the histological type of the mass.[2,7,8] Frozen section is performed by freezing the tissue portion in a cryostat machine and then being stained.[9] Frozen section allows surgeons to decide whether to perform extensive resection or not.[8,9] However, more accurate diagnosis of histological type and degree is achieved by using paraffin block.[2,3,8]

Many studies have confirmed the accuracy of frozen section diagnosis for assessment of ovarian neoplasms with acceptable sensitivity (71-97%) and specificity of more than 95%.[10-14] The limitations of frozen section procedure are mostly for borderline, mucinous and large tumors. Frozen section is most reliable for small serous tumors.[10,15,16] Several factors can affect the accuracy of frozen section diagnosis, such as patient characteristics, tumor size, histological type, and the pathologist's experience.[10,15] Histological typing of ovarian neoplasm followed the International Federation of Gynecology and Obstetrics (FIGO) recommendations.[17] The accuracy of frozen section for ovarian neoplasm has not been reported yet in our hospital, so we would like to evaluate the accuracy of frozen section for ovarian neoplasm in our hospital.

## METHODS

A retrospective evaluation was conducted on medical records of patients with ovarian neoplasms who underwent a frozen section laparotomy between the years 2008-2013 at Dr. Cipto Mangunkusumo Hospital. Records with incomplete data on frozen section or paraffin block report were excluded. Criteria for frozen section laparotomy in our facility was based on a Malignancy score of equal to or more than 6. The malignancy score is made up of five parameters; 10% drop in body weight over the last 3 months, ascites, resistive index (RI) less than 0.4 on ultrasound, solid mass on ultrasound, and CA125 level of over 135. Each, if present, gets a score of 2. A score ≥ 6 indicates suspicion for malignancy.[6]

For histologic examinations, once tumor is removed, 2-5 tissue samples are taken from parts of the mass that appear irregular. Frozen sections are immediately studied and reported. Paraffin block examinations are conducted according to the standard. Histology reports that were recorded were classified into benign, borderline and malignant. Results of the frozen section were then compared to results from the paraffin block. Paraffin block is more accurate for histological type and grade compared to frozen section. For the purpose of this study, the final histopathological diagnose was assumed to be correct.

Descriptive statistics were obtained and sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

## RESULTS

We found a total of 139 records of patients who underwent laparotomy for presumed malignant ovarian neoplasm in the years 2008-2013. In 37 cases, frozen section was not done, and in 11, paraffin block results were not available. Ninety-one cases were analyzed. The mean age was 45.02 ± 10.8, with the youngest being 18 years old and the oldest 65 years old. The final histopathologic report is described in Table 1.

Final histopathology results showed 11 patients with no malignancy, 14 patients with borderline tumor and 48 patients with cystoadenocarcinoma.

The frozen section results were 14 (15.4%) benign, 14 (15.4%) borderline and 63 (69.3%) malignant. The final histopathologic diagnosis comprised of 11 (12.1%) benign, 13 (14.3%) borderline, and 67 (73.7%) malignant cases. The overall accuracy of frozen section diagnosis was 87.9%, calculated from the total cases correctly diagnosed over the total number of cases. The paraffin result was worse than the frozen section result in 8.7% and better in 3.2% of cases.

The sensitivity, specificity, PPV and NPV were analyzed (Table 3). The sensitivity of frozen section diagnosis is 81.8% for benign, 76.9% for borderline, and 91.0% for malignant. Specificity value for benign, borderline and malignant tumors were 93.8%, 94.8%, and 91.6%, respectively.

The results were later analyzed for area under the ROC curve, which proved that frozen sections are useful in diagnosing malignancies (AUC >0.8).

**Table 1.** Final Histopathology Report.

| Histotype | Frequency | Percent (%) |
|---|---|---|
| Non Malignancy | 11 | 12.1 |
| Serous Cystoadenoma Borderline | 5 | 5.5 |
| Mucinous Cystoadenoma Borderline | 7 | 7.7 |
| Endometrioid Cystoadenoma Borderline | 1 | 1.1 |
| Clear Cell Cystoadenoma Borderline | 1 | 1.1 |
| Serous Cystoadenocarcinoma | 11 | 12.1 |
| Mucinous Cystoadenocarcinoma | 9 | 9.9 |
| Endometrioid Cystoadenocarcinoma | 10 | 11.0 |
| Clear Cell Cystoadenocarcinoma | 18 | 19.8 |
| Adenofibroma Cyst | 1 | 1.1 |
| Granulosa Cell Tumor | 5 | 5.5 |
| Endodermal sinus (yolk sac) tumor | 3 | 3.3 |
| Ovarian Fibroma | 1 | 1.1 |
| Dysgerminoma | 3 | 3.3 |
| Immature Teratoma | 5 | 5.5 |
| Total | 91 | 100,1 |

**Table 2.** The Results of Frozen Section and Paraffin Sections in Various Categories of Ovarian Neoplasms (n=91)

| | | Paraffin | | | |
|---|---|---|---|---|---|
| | | Benign | Borderline | Malignant | Total |
| Frozen Section | Benign | 9 | 2 | 3 | 14 |
| | Borderline | 1 | 10 | 3 | 14 |
| | Malignant | 1 | 1 | 61 | 63 |
| | Total | 11 | 13 | 67 | 91 |

**Table 3.** Sensitivity, Specificity, PPV and NPV of Frozen Sections (%)

| | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | AUC |
|---|---|---|---|---|---|
| Benign | 81.8 | 93.8 | 64.2 | 97.5 | 0.87 |
| Borderline | 76.9 | 94.8 | 66.6 | 96.1 | 0.85 |
| Malignant | 91.0 | 91.6 | 96.8 | 78.5 | 0.91 |

## DISCUSSION

Intraoperative frozen section has been used to diagnose ovarian neoplasm for a considerable time. Intraoperative diagnosis can dictate the extent of surgery; therefore its accuracy is very important. Many studies have confirmed the accuracy of frozen section diagnosis for the assessment of ovarian neoplasms with acceptable sensitivity (71-97%) and specificity of more than 95%.[10-14] Various studies have shown that the overall accuracy of frozen sections range from 86%-97%.[3,7] In this study, we found that the overall accuracy of intraoperative frozen section in our facility was adequate, at 87.9%.

The procedure fared well in terms of sensitivity, specificity, PPV and NPV. A meta analysis found that sensitivity of frozen section for benign and ma-

lignant lesions are 65-97% and 71-100% respectively, and specificity are 97-100% and 98.3-100% respectively.[2,3,7] In our study, we found that sensitivity for benign and malignant lesions to be 81.8% and 91.0%, respectively. However, specificity was lower at 91.0% and 91.66% for benign and malignant lesions, respectively.

This test proved to be great for detecting malignant lesion (AUC 0.9). However, PPV for benign tumors was low at 64.3%, indicating that there was a 1 in 3 possibility that a frozen section diagnosis of benign lesion will return with a borderline or malignant histopathology. In this study, 14.2% (n=2) benign diagnosis from frozen section was found to be borderline and 21.4% (n=3) found to be malignant. This was correlated to the relatively low NPV for malignant diagnosis. On the other hand, over-diagnosis of benign cases as borderline and malignant was 0.9% (n=1) each. This may be due to the low number of benign cases, as predictive values are related to prevalence. It is further precipitated by the fact that frozen sections are generally done when there is preoperative suspicion of malignancy. Until proven, however, the concern for underdiagnosis must be implied in practice and patients with benign frozen section results must be followed up until their final diagnosis is established.

Consistent with other studies, frozen section shows the lowest sensitivity for borderline tumors.[2-4] In this study, the sensitivity and specificity are 76.9% and 94.8%, respectively. Of 14 borderline frozen section results, three were later diagnosed as malignant, and one as benign. There is a recurring trend for underdiagnosis, which may be attributable to low prevalence of borderline cases. On the other hand overdiagnosis was rare, with one case (9.0%) of benign tumor detected as borderline and malignant each, and one case (7.6%) of borderline tumor detected as malignant.

## CONCLUSION

In conclusion, we found that the accuracy of intraoperative frozen section in our facility is adequate to diagnose ovarian neoplasm, and can be used to assist in determining the extent of surgical management. Further research with a larger sample and comparing patient characteristics to the accuracy of frozen section is needed to increase the understanding of factors affecting frozen section accuracy.

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Research Article

# p53 Gene Codon 72 Polymorphisms among Cervical Carcinoma Patients

## *Polimorfisme Gen p53 Kodon 72 pada Penderita Karsinoma Serviks yang Dirawat*

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## Abstract

**Objective:** To identify the association between p53 gene codon 72 polymorphism and cervical carcinoma.

**Method:** An analytic observational study with case-control design, from November 2013 until March 2014 in the Department of Obstetrics and Gynecology and Microbiology Laboratory Faculty of Medicine, Sriwijaya University, Dr. Moh. Hoesin Hospital Palembang.

**Result:** In total there are 100 samples analyzed consisting of 50 subjects and 50 control groups. Genotype distribution in subject group are 54% Arg/Arg, 42% Pro/Arg and 4% Pro/Pro, and in control group are 36% Arg/Arg, 46% Pro/Arg and 18% Pro/Pro. Arg/Arg genotype is at risk of cervical carcinoma 6.7 times higher compared with Pro/Pro genotype (p=0.013; OR 6.75; 95% CI 1.34-34.94). Arg allele in the p53 gene codon 72 increase the risk of cervical carcinoma 2.6 times more than Pro allele.

**Conclusion:** Proline mutation to Arginine in gene p53 P72R is one of the risk factor for cervical carcinoma.

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**Keywords:** arginine, cervical carcinoma, gene p53 codon 72, polymorphism, proline

## *Abstrak*

***Tujuan:*** *Mengetahui hubungan antara polimorfisme gen p53 kodon 72 dan karsinoma serviks.*

***Metode:*** *Penelitian observasional analitik dengan desain studi kasus-kontrol. Dilakukan dari November 2013 sampai dengan Maret 2014 bertempat di Departemen Obstetri dan Ginekologi Rumah Sakit Dr. Mohammad Hoesin Palembang dan Laboratorium Mikrobiologi Rumah Sakit Dr. Moh. Hoesin Palembang.*

***Hasil:*** *Penelitian diikuti oleh 100 subjek yang memenuhi kriteria inklusi, masing-masing 50 subjek pada kelompok kasus dan kontrol. Distribusi genotipe gen p53 kodon 72 pada kelompok kasus adalah Arg/Arg 54%, Pro/Arg 42% dan Pro/Pro 4% sedangkan pada kelompok kontrol Arg/Arg 36%, Pro/Arg 46% dan Pro/Pro 18%. Genotip Arg/Arg memiliki risiko 6,7 kali lebih besar untuk terjadi karsinoma serviks dibandingkan dengan genotip Pro/Pro. Adanya alel Arg pada gen p53 kodon 72 meningkatkan risiko terjadinya karsinoma serviks 2,6 kali lebih besar dibandingkan alel Pro.*

***Kesimpulan:*** *Mutan Prolin menjadi Arginin pada polimorfisme gen p53 P72R merupakan faktor risiko terjadinya karsinoma serviks.*

*[Maj Obstet Ginekol Indones 2015; 3: 165-169]*

***Kata kunci:*** *arginin, gen p53 kodon 72, karsinoma serviks, polimorfisme, prolin*

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## INTRODUCTION

Cervical carcinoma is the most common gynecological malignancy and the second most common malignancies in women worldwide. Data from the Department of Anatomical Pathology Faculty Of Medicine, Sriwijaya University RSMH Palembang also places cervical carcinoma as the second most common malignancy in women, after breast malignancy.[1-4]

Although the role of HPV in cervical cancer carcinogenesis has been proven, only a few of HPV infection will develop into cervical carcinoma. This suggests possibility of other influences that might be involved in the development of cervical carcinoma, one of them is genetic factor. Mutation of the p53 gene is one of the genetic variations associated with the occurrence of malignancy.[5-7]

P53 gene is a tumor suppressor gene that plays a role in response to stress in order to maintain genomic stability, responds to DNA damage, hypoxia, metabolic stress and activation of oncogenes. Single nucleotide polymorphisms (SNPs) of p53 gene codon 72 will produce two types of alleles, namely Arginine (p53-R72) or Proline (p53-P72) at the structure of the amino acid at codon 72. According to Storey, women who are homozygous for Arginine at codon 72 of p53 gene are seven times more likely to be exposed to cervical cancer.[6,9-11]

Comparative sequence analysis of non-human primates demonstrated that p53-P72 is the wild type, although the number of p53-R72 population is quite enough (>50%). The frequency of homozygous Arginine in certain ethnicity is between 12.4% and 53.4%. Beckman and his colleagues were the first to demonstrate the difference in allele frequency distribution between the R72 and P72 in Nigerian population (black Africans) and Sweden (Europe West), amounting 17 percents and 63 percents of the population.[6,9,11-12]

Variation of the allele frequency in some ethnicities may cause differences in research result about relationship between p53 codon 72 polymorphism and cervical carcinoma in several countries. Research in Sweden, Chile, Peru, China and India supported these findings.[5,8,13-16] However, studies in Netherlands, USA, Poland, Italy, Korea, Japan and Thailand are contradictory.[17-26] In Palembang, there is no data about codon 72 allele of the p53 gene and its association with carcinoma of the cervix, so it is necessary to identify the association between p53 codon 72 polymorphism and cervical carcinoma in Palembang population.

## METHOD

This is an analytical observational research with case control study design. This study is conducted at the Department of Obstetrics and Gynecology and Microbiology Laboratory of Faculty of Medicine Sriwijaya University in Dr. Mohammad Hoesin Hospital Palembang, which started from November 1st 2013 until March 31st 2014.

Populations of this study are patients who are diagnosed with cervical carcinoma who came to the outpatient clinic and any hospitalized patient in obstetric and gynecology department of RSMH Palembang. Sampling is done by quota sampling technique, until total subjects in the experimental group and control group reach 50 patients.

The inclusion criteria for the experimental group are patients who are diagnosed with cervical carcinoma, which is proved by histopathology result and patient's willingness to join the research by signing the informed consent form. For the control group, inclusion criteria are patients who came to gynecology outpatient clinic or who has been hospitalized in in-patient installation of obstetric and gynecology department of RSMH Palembang who is not diagnosed or suspected to have neoplasm or another malignancy diseases, no precancerous lesion Pap Smear examination or suspected to have cervical carcinoma and patient's willingness to join the research by signing the informed consent form.

Exclusion criteria for case group are patients who have been diagnosed or suspected to have other malignancy or if patient are not willing to join the research. For the control group, criteria were precancerous lesion in Pap's Smear result or suspected cervical carcinoma patients who refuse to join the research.

## RESULT

Table 1 shows the socio-demographic and clinical characteristic of research subjects.

**Table 1.** Socio-demographic and Clinical Characteristic.

| Characteristic | Case | Control | p |
|---|---|---|---|
| Median age | 49 ± 8.8 | 38.8 ± 9.5 | < 0.0001 |
| Median BMI | 23.22 ± 4.90 | 21.64 ± 31.08 | 0.058 |
| Domicile | | | |
| Urban area | 31 | 41 | 0.03 |
| Rural area | 19 | 9 | |
| Ethnic group | | | |
| Sumatera | 33 | 42 | 0.038 |
| Non-Sumatera | 17 | 8 | |
| Education | | | |
| Uneducated | 5 | 0 | < 0.0001 |
| Elementary | 14 | 1 | |
| Junior high | 14 | 6 | |
| Senior high | 16 | 22 | |
| Bachelor | 1 | 21 | |
| Occupation | | | |
| Housewife | 38 | 22 | < 0.0001 |
| Civil servant | 1 | 27 | |
| Others | 11 | 1 | |
| Smoking history | | | |
| Yes | 2 | 2 | 1.00 |
| No | 48 | 48 | |
| Contraception history Oral | | | |
| Yes | 9 | 4 | 0.23 |
| No | 41 | 46 | |
| First sexual activity | | | |
| < 20 years old | 33 | 8 | < 0.001 |
| ≥ 20 years old | 17 | 42 | |
| Marriage history | | | |
| 1 time | 6 | 2 | 0.27 |
| > 1 time | 44 | 48 | |
| Parity total | | | |
| ≥ 7 | 8 | 0 | < 0.001 |
| < 7 | 42 | 50 | |

The youngest age in this research is 19 years old and the oldest subject is 73 years old. There is a significant difference in median age, domicile distribution, ethnic group and occupation between the case and control group.

Age of first sexual activity and total parity are important clinical risk factors for cervical carcinoma. However smoking, oral contraception, and marriage status showed no significant correlation with the incidence of cervical carcinoma. The clinical characteristics of the research subjects are presented on the table above.

In this research gene p53 codon 72 is obtained through DNA extraction process and PCR-RFLP method from blood sample. Polymorphism in gene p53 codon 72 is recognized with BstUI enzyme. Figure 1 showing the PCR-RFLP result example. Genotype appearance of wild type Pro/Pro (1 band with fragment length 199 bp) is showed in subject number 46. Subject number 50 has mutant genotype Arg/Arg (2 bands with fragment length 113 bp and 86 bp). Subject number 47, 48 and 49 exhibit mutant heterozygote genotype appearance of Pro/Arg (3 bands with fragment lengths of 199 bp, 113 bp and 86 bp).

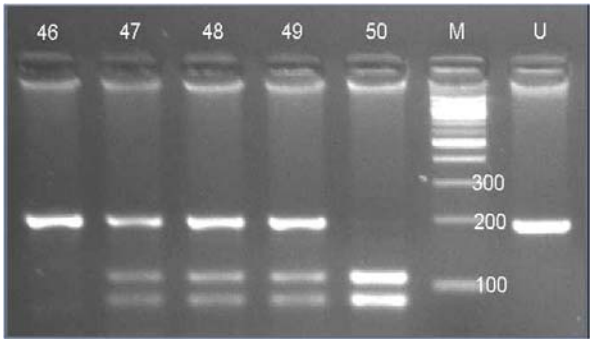


**Figure 1.** Example of PCR-RFLP Result Gene p53 Codon 72 with BstUI Restriction Enzyme.

Genotype distribution in case group is Arg/Arg 54%, Pro/Arg 42% and Pro/Pro 4%. The distribution of genotype in control group is Arg/Arg 36%, Pro/Arg 46% and Pro/Pro 18%. In general, the distribution of genotype Arg/Arg, Pro/Arg and Pro/Pro are 45%, 44% and 11% respectively. From the whole subjects, Arg allele percentage is 67% and Pro allele is 33%.

Statistic analysis with Chi square test is done to determine the correlation between polymorphism gene p53 codon 72 and cervical carcinoma. There is a significant increase in the risk of cervical carcinoma for individual with homozygote mutant genotype (Arg/Arg) compared with individual with wild type genotype (Pro/Pro) on gene p53 codon 72 (p=0.013; OR 6.75; 95% CI 1.34-34.94). Allele analysis showed women who has Arginine allele in the p53 gene codon 72 is at risk of cervical cancer 2,6 times greater than women with Proline allele (OR 2.61; 95% CI 1.40-4.88).

**Table 2.** Correlation of Genotype p53 Gene Codon 72 and Carcinoma Cervix

| | | Case | | Control | | p |
|---|---|---|---|---|---|---|
| | | N | % | N | % | |
| Genotype | Arg/Arg | 27 | 54 | 18 | 36 | 0.013* |
| | Pro/Arg | 21 | 42 | 23 | 46 | 0.097** |
| | Pro/Pro | 2 | 4 | 9 | 18 | Ref |
| Total | | 29 | 100 | 27 | 100 | |

## DISCUSSION

Epidemiological data shows that most cervical carcinoma is found in young women. Median age of this finding is 52 years old with distribution peak at age of 35-39 years old and 60-64 years old.[1,3] Concurrent with previous literature, median age of the case group (cervical carcinoma) in this research is 49.8 ± 8.8 years old.

In this research, there is a significant difference in domicile, education level, job and ethnic group between case group and control group. Whereas median body mass index (BMI) in this research subject found no differences between both groups. Socioeconomic factor is related with carcinoma cervix. The majority of carcinoma cervix patients came from low socioeconomic who has no access to routine gynecology examination.[1,3] Reis et al discovered that individual with high education level has lower risk of cervical carcinoma(OR 0.18). They suggested that low education level is related with an increase of sexual activity on young age, numerous sexual partners and bad genital hygiene.[27]

Statistically in this research there is no significant correlation between smoking history and cervical carcinoma. This result is different with meta-analysis about correlation between smoking and cervical carcinoma by Gandini et all. They concluded that active smokers are at increased risk of contracting cervical squamous cell carcinoma (RR 2.03; 95% CI 1.31-4.04), whereas risk among ex-smoker is relatively lower at 1.80 (95% CI 0.95-3.44).[28]

Reproductive history is also affects the risk of cervical carcinoma. Analysis result in this research also shows significant correlation between parity ≥7 and cervical carcinoma (p=0.006). Women who has parity ≥7 times has 2 times the risk to have carcinoma cervix (OR 2.19; 95% CI 1.75-2.74).

Median age of first sexual activity in the case group in this research is 19.12±3.98 years old. This median age is lower than the control group. Statistical analysis shows an increased risk of cervical carcinoma 10 times higher than women who have their first sexual activity before the age of 20 is 10.19 (95% CI 3.92-26.51).

Oral contraception combination pill usage can be a risk factor of cervical carcinoma. Research from Moreno et all show an odds ratio of 2.82 (95% CI 1.46-5.42) for contraception usage 5-9 years and 4.03 (95% CI 2.09-8.02) for usage ≥10 years.[1,3,27,29,30] However in this research, there is no significant correlation between oral contraception and cervical carcinoma (p=0.23).

Comparative sequence analysis to primate except human shows that p53-R72 is a wild type, even though p53-R72 in population is varied (>50%). Data from various ethnicities shows Arginine homozygous frequency is between 12.4% till 53.4%.[6,9,27,31] Genotype distribution pattern and allele in this research is similar with Andersson's research in Sweden and Ojeda's in Chile; the only difference is the lower genotype distribution of wild type.[5,13]

Chi square test done between gene genotype p53 codon 72 and cervical carcinoma concludes that there is an increasing risk of cervical carcinoma 6.7 times for individual with homozygote mutant genotype (Arg/Arg) compared with individual with wild type genotype (Pro/Pro) for gene p53 codon 72 (OR 6.75; 95% CI 1.34-34.94). Individuals with heterozygote mutant genotype (Pro/Arg) have no significant risk when compared with women with wild type genotype (p=0.079). Allele analysis shows significant result for allele Arg to p53 gene codon 72, which will increase the risk of carcinoma cervix 2.61 times higher than allele Pro (p=0.02; OR 2.61; 95% CI 1.40-4.88).

Some of supporting researches have various odds ratio (OR) result. Meta-analysis by Jee et al in 2004 shows that the odds ratio (OR) of women with cervical carcinoma with homozygote mutant (Arg/ Arg) compared with heterozygote mutant (Arg/ Pro) in general is 1.2 (1.1-1.3; p<0.001).[32]

Some of the researches also relates polymorphism p53 codon 72 with prognosis and response to therapy. Individual with genotype R72 has a higher risk and better quality of life after receiving chemotherapy or radiation therapy. Similar results are also found in cancer of head and neck, breast and lung.[9]

## CONCLUSION

Proline mutation to Arginine in gene p53 P72R is a risk factor for cervical carcinoma.

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Research Article

# Effect of Smoking on Advanced Stage Cervical Cancer Patient Survival

## *Pengaruh Merokok pada Kesintasan Pasien Kanker Serviks Stadium Lanjut*

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## Abstract

**Objective:** The researchers aim to investigate the relationship between smoking habit and other factors as prognostic factors of cervical cancer.

**Method:** We performed a retrospective and prospective cohort study with subjects that are stage IIB-IVB cervical cancer patients in Dr. Cipto Mangunkusumo Hospital followed up from August 2009 to April 2014. The subjects'medical records were reviewed, and patients were interviewed about their current condition by telephone. Questions asked include smoking habit, spouse's smoking habit, and mortality status. Patients that could not be contacted by phone were excluded from the study. Statistical analysis was done using Stata 10.

**Result:** Out of 390 cervical cancer patients stage IIB-IVB in 2009, there were 270 patients (69.2%) that were included in the inclusion criteria. Most of the patients are 40-59 years old (82.2%) and are non-smokers (91.8%). The most frequent clinicopathological characteristic is IIIB (63.3%) and squamous cell carcinoma (71.9%). The 5-year survival rate is 22.6%. There is no statistical significance between advanced stage cervical cancer survival with the patients' or patients' husbands' smoking habit.

**Conclusion:** In our study, smoking habits do not aggravate survival rate of advanced stage cervical cancer patients but further research must be done with more sample. Stage, and tumor size both by physical examination and ultrasound can be used as the prognostic factor.

[Indones J Obstet Gynecol 2015; 3: 170-176]

**Keywords:** Brigmann Index, cervical cancer, smoking, survival

## *Abstrak*

***Tujuan:*** *Mengetahui pengaruh merokok terhadap faktor prognosis kanker serviks serta faktor-faktor lain yang berhubungan sehingga dapat membantu memberikan gambaran mengenai prognosis kanker serviks.*

***Metode:*** *Penelitian ini adalah kohort retrospektif. Sampel penelitian adalah pasien kanker serviks stadium IIB-IVB di RS Dr. Cipto Mangunkusumo mulai dari Agustus 2009 sampai April 2014. Kondisi terakhir pasien di follow up menggunakan telepon. Kondisi yang dinilai adalah pasien masih hidup atau tidak, pasien merokok atau tidak, dan suami pasien merokok atau tidak. Pasien yang tidak dapat dihubungi akan dieksklusi dari penelitian. Analisa data menggunakan Stata 10.*

***Hasil:*** *Dari 390 pasien kanker serviks stadium IIB-IVB, hanya 270 pasien (69,2%) yang memenuhi criteria inklusi dan eksklusi. Sebagian besar pasien berusia 40-59 tahun (82,2%), tidak merokok (91,8%), suami merokok (73,3%). Karakteristik kliniko patologis yang terbanyak adalah stadium IIIB (63,3%), jenis karsinoma skuamosa (71,9%). Kesintasan 5 tahun pasien kanker serviks adalah 22,6%. Hubungan antara kebiasaan merokok pasien dan suami dibandingkan dengan kesintasan pasien kanker serviks menunjukkan hasil yang tidak signifikan.*

***Kesimpulan:*** *Dalam penelitian kami, kebiasaan merokok tidak memperburuk tingkat kelangsungan hidup penderita kanker serviks stadium lanjut, tetapi penelitian lebih lanjut harus dilakukan dengan jumlah sampel lebih besar. Stadium, dan ukuran tumor baik dengan pemeriksaan fisik dan USG dapat digunakan sebagai faktor prognostik.*

*[Maj Obstet Ginekol Indones 2015; 3: 170-176]*

***Kata kunci:*** *kanker serviks, merokok, Indeks Brigmann, kesintasan*

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## INTRODUCTION

The mortality and morbidity rate of cervical cancer globally is 275.000 and 529.000, respectively, making it the third leading cancer globally and the first leading cancer in developing country.[1-4] Smoking has been a well-known risk factor for cervical cancer. According to the WHO in 2008, Indonesia is the third leading country in number of smoker globally, with 59.8 million smokers (approximately 225 billion cigarettes per year), and 2.7% of them are women. It is estimated that each year there are 2,3 million Indonesian women who are active smokers while another 1.6 million women are non-cigarette tobacco users. Tobacco contains carcinogenic material; burned tobacco produces polycyclic aromatic hydrocarbon heterocyclic nitrosamines, which gives negative effects to people who consume it.

The role of smoking habit as prognostic factor for cervical cancer patients in Dr. Cipto Mangunkusumo Hospital has not been established yet. The

most well known prognostic factor for cervical cancer patient is its stage. Other prognostic factors contributing to cervical cancer patient outcome is important to be investigated. Therefore, the study aims to investigate the relationship between smoking and other factors as prognostic factors of cervical cancer.

## METHODS

The study uses cohort retrospective method. Subjects are patients from Dr. Cipto Mangunkusumo Hospital with advanced stage (Stage IIB-IVB) cervical cancer from August 2009 - April 2014. Demographic and clinicopathological characteristics were obtained from medical record. Patients were contacted via telephone, from numbers listed on the medical record, and asked their mortality status, smoking habit and husband's smoking habit. Exclusion criteria include patients who could not be contacted by telephone. Patients' survival rate was calculated by finding the interval (in days) between date of death and date of diagnosis. Outcome measure is survival rate, which is determined by months after diagnosis. The follow up period is 58 months, therefore survival until the end of the follow up period is considered as 5-year survival rate. Statistical analysis was done using Stata 10.

## RESULTS

Among 390 patients with cervical cancer stage IIB-IVB in RSCM since August 2009, 270 (69.2%) patients were successfully interviewed by phone. Sixty five percent of these patients were referred by rural hospital, 28.1% patients were referred by gynecologist and rest of them were referred by primary health care centers. Occupation of the subjects was mostly (85.2%) housewives. Patients were divided into ages above 60 years old (10.4%), between 40-59 years old (82.2%) and below 40 years of age (7.4%). While, the age of cervical cancer onset were found mostly in the 40-59 age group with 65% belonging to this group. Most of the patients (41.1%) has an undergraduate degree, and 64.1% had 3 children or more. 89.3% of the patients never had a pap smear examination before.

The physical examination showed that most of the subjects (80%) had tumors sized 4-8 centimeters, and rest (15.2%) had tumors less than 4 cm. On ultrasonography findings, only 66.7% of the patients had 4-8 centimeters tumor. Patients were also classified into The International Federation of Gynecology and Obstetrics (FIGO) stages, results were as follows: IIB: 22.2%, IIIA: 4.8%, IIIB: 63.3%; and IVA: 9.6%. 85% patients didn't have any pelvic lymph node enlargement. From histopathology findings, most patients (71.9%) were found to have squamous cell carcinoma (SCC) histological subtype; with 66.6% of them being moderately differentiated and 16.7% being well differentiated. 81.3% of the subjects' tumor cells were not keratinized, and no lymphovascular invasion was found in 86.7% of patients. Therapy modalities were mostly radiotherapy (42.2%) and chemoradiation with cisplatin-ifosfamide (30%).

The patients were then divided into the light, moderate and heavy smoker based on the Brigmann's Index. Only 8.2% (n=8) of patients admitted to be a smoker while the rest claim to not smoke; 73.3% of the subjects' spouses were smokers.

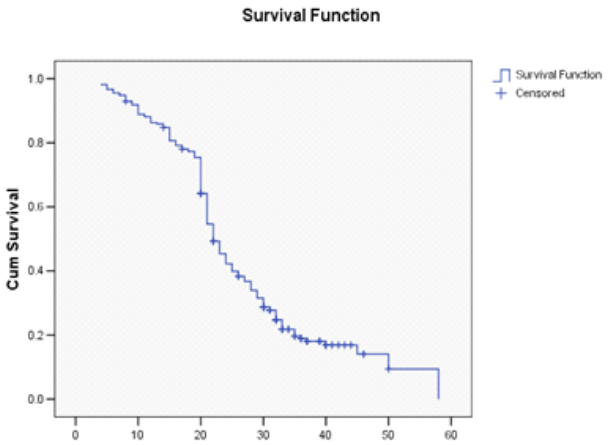


**Figure 1.** Advance Stage Cervical Cancer 5-years Survival Rate.

The average survival rate amongst patients was 22 months (SD= 4-58). While those who made it until the end of the follow up period (5-year survival rate) of advanced stage cervical cancer patients was 22.6%. The study showed that survival in the first year was 86.3%, decreasing to half in the second year to 43.3%, and kept decreasing to 24.4%, 23.3%, and 22.6% for the third, fourth, and fifth year, respectively.

Bivariate analysis showed no statistically significant relationship between the size of the tumor, lymphadenopathy, cell differentiation, lymphovascular invasion, keratinization stage of cervical cancer, and response to therapy with smoking status of both the patient and the husband.

**Table 1.** Bivariate Analysis of the Relationship between Prognostic Factor and Survival

| | B | p | HR | 95%CI | |
|---|---|---|---|---|---|
| | | | | Lower limit | Upper limit |
| Age | -0.161 | 0.317 | 0.852 | 0.622 | 1.167 |
| Parity | -0.059 | 0.599 | 0.942 | 0.755 | 1.176 |
| Pap Smear | 0.144 | 0.504 | 1.155 | 0.757 | 1.762 |
| Tumor size | 0.247 | 0.104 | 1.281 | 0.950 | 1.726 |
| Tumor size USG | 0.561 | <0.001 | 1.752 | 1.354 | 2.267 |
| Cancer stage | 1.518 | <0.001 | 4.564 | 3.527 | 5.906 |
| Pelvic lymph node | -0.148 | 0.458 | 0.863 | 0.584 | 1.274 |
| Histopathology | 0.054 | 0.486 | 1.056 | 0.906 | 1.229 |
| Cell differentiation | 0.152 | 0.008 | 1.164 | 1.041 | 1.302 |
| Lymphovascular invasion | 0.251 | 0.220 | 1.285 | 0.860 | 1.919 |
| Brigmann Index | -0.029 | 0.874 | 0.972 | 0.679 | 1.389 |
| Brigmann Index Patient Husband | 0.072 | 0.282 | 1.075 | 0.942 | 1.227 |
| Keratinization | 0.192 | 0.236 | 1.212 | 0.882 | 1.666 |
| Therapy response | 0.261 | 0.066 | 1.299 | .982 | 1.717 |

Table 1 shows that there is a significant relationship between cervical cancer survival rate with the prognostic factors: tumor size, cell differentiation, lymphovascular invasion, keratinization, stage of cervical cancer, and response to therapy based on p-value<0.25. thus, a multivariate analysis was done revealing that stage and tumor size has a statistically significant relationship with survival of cervical cancer.

**Table 2.** Multivariate Analysis of the Relationship between Prognostic Factors and Survival

| | B | p | HR | 95%CI | |
|---|---|---|---|---|---|
| | | | | Lower limit | Upper limit |
| Tumor size < 4 cm | | 0.122 | | | |
| Tumor size 4-8 cm | 0.366 | 0.043 | 1.441 | 1.011 | 2.054 |
| Tumor size > 8 cm | 0.337 | 0.272 | 1.400 | 0.768 | 2.555 |
| Cell diff Good | | 0.885 | | | |
| Cell diff Medium | -0.075 | 0.726 | 0.928 | 0.612 | 1.409 |
| Cell diff Bad | 0.041 | 0.900 | 1.042 | 0.551 | 1.970 |
| Cell diff Good + Medium | 0.164 | 0.580 | 1.178 | 0.659 | 2.107 |
| Cell diff Medium + Bad | -0.113 | 0.706 | 0.894 | 0.498 | 1.604 |
| Lymphovascular invasion | -0.096 | 0.675 | 0.908 | 0.580 | 1.423 |
| Keratinization | 0.235 | 0.220 | 1.265 | 0.869 | 1.841 |
| Stad IIB | | <0.001 | | | |
| Stad IIIA | 3.182 | <0.001 | 24.084 | 7.420 | 78.174 |
| Stad IIIB | 3.704 | <0.001 | 40.607 | 14.757 | 111.740 |
| Stad IVA | 5.113 | <0.001 | 166.128 | 55.508 | 497.202 |
| Therapy response Complete | | 0.419 | | | |
| Therapy response Partial | 0.154 | 0.307 | 1.167 | 0.868 | 1.568 |
| Therapy response Progressive | 0.379 | 0.313 | 1.461 | 0.700 | 3.051 |

The Kaplan-Meier's curve supports the result of the multivariate analysis. The curve shows that tumor size and stage of cervical cancer are associated with 5-year survival. Patients with 4-8 centimeters sized tumors were 1.441 times less likely to survive than tumors sized <4 centimeters. A confidence interval of 99.5% shows that there is a statistically significant association between cervical cancer stage and 5-year survival rate.

There is no significant difference in the correlation between active and passive smokers status (based on Briggman index) with 5-year survival rate analyzed using the Cox regression. This was shown every year during the follow-up period (first to fifth year).

## DISCUSSION

In Indonesia, most cases of cervical cancer is found in its advanced stage, most commonly stage III.[5] Based on INASGO Cancer Registry Reports, advanced stage cervical cancer (IIB-IVA) cases in Dr. Cipto Mangunkusumo Hospital has reached 71.2% of all cases of cervical cancer in 2013.[6] Cervical cancer survival rate is mainly influenced by the size of the tumor and metastatic organ involvement.[7] Overall, cervical cancer survival rate will worsen as cancer stage increases, regardless of other prognostic factors such as type of therapy or comorbidities.[8-10]

Five-year survival rate in cervical cancer based on stage is as follows: IA: 93%, IB: 80%, IIA: 63%, IIB: 65.8%, IIIA: 39.7%, IIIB: 41.5%, IVA: 22.0%, and IVB: 9.3%.[8-10] This is consistent with our study (p<0.001). The method used in this study was a retrospective and prospective cohort. Patients were phoned to obtain smoking status and were followed up for 58 months using a prospective cohort method to calculate survival rate.

Aside from being a risk factor for cervical cancer, smoking also contributes to lower survival rate.[11,12] The mechanism of the detrimental effects of smoking on the incidence of cervical cancer still remains unclear. However, it is believed, cigarettes suppresses the immune system against HPV infection making patients more prone to infection.[13,14] In addition, smoking causes remodeling of cervical epithelium[13] and disrupts tissue oxygenation which impacts the usage of radiation therapy.[12] Waggoner et al, stated that the prognosis of cervical cancer patients who underwent chemoradiation therapy are poorer in smoking patients compared to non-smokers patients.[12] However, in this study, smoking did not show significant differences on cervical cancer survival rate. Supporting our study, Fyles et al argues that there is no significant difference between smoking and levels of tissue oxygenation in patients with cervical cancer.[15] Our study showed the proportion of cervical cancer patients who smoke is 8.2% compared to 91.8% who do not smoke. The low amount of patients who smokes could be a contribution to why our study shows that there is no significant relationship between smoking and cervical cancer survival rate.

The effect of being a passive smoker on the survival rate of cervical cancer is still debatable. A research in China by Cheng et al. concluded that

**Table 3.** Correlation Patient Smoking Status with 5-years Survival of Cervical Cancer

| | B | p | HR | 95%CI | |
|---|---|---|---|---|---|
| | | | | Lower limit | Upper limit |
| Brigmann Index 0 | | 0.828 | | | |
| Brigmann Index 1 - 200 | 0.097 | 0.720 | 1.102 | 0.649 | 1.872 |
| Brigmann Index 200-600 | -0.245 | 0.628 | 0.783 | 0.291 | 2.107 |

**Table 4.** Correlation Patient Husband Smoking Status with 5-years Survival of Cervical Cancer

| | B | p | HR | 95%CI | |
|---|---|---|---|---|---|
| | | | | Lower limit | Upper limit |
| Brigmann Index 0 | | 0.382 | | | |
| BrigmannIndex 1-200 | 0.254 | 0.198 | 1.289 | 0.876 | 1.899 |
| BrigmannIndex 200-600 | 0.300 | 0.096 | 1.350 | 0.948 | 1.924 |
| BrigmannIndex > 600 | 0.135 | 0.577 | 1.144 | 0.713 | 1.836 |

smoking women have a 73% increased risk for cervical cancer.[16]

Furthermore, this is clarified by Louis et al in their study which described that the risk only occur to women with active smoking habits.[17] Their research concluded that passive smoking factor could not be the only deciding factor on whether one could have cervical cancer. 73.3% of subjects in our research are passive smokers. However, a flaw in our method was that the passive smoker patients were not asked the amount of exposure to cigarette smoke. Currently, the authors could not find any other researches investigating the correlation between passive smoking and cervical cancer survival rate and further research with a larger sample size is needed.

Various studies reveal that age is one of the prognostic factors for cervical cancer survival rate, but the significance of age as the sole determinant remains unknown.[17-20] In this study, age shows no significant association (p=0.317) with the prognosis of advanced stage cervical cancer. This is consistent with Kumari et al,[21] which showed that the age of patients has no significant correlation as a prognostic factor of cervical cancer. This could be due to most of our subjects (82.2%) are between the ages 40-59 years old. According to literature, age only affects survival rate of cervical cancer in patients younger than 35 years old and older than 70 years old.[20-23]

Another factor investigated in our study is the association of multiparity with the incidence of cervical cancer. We found significant relationship between parity and cervical cancer survival rate (p-value = 0.599). However, studies have shown that it is highly correlated.[24,25] According to a multicenter study, by Muñoz et al[25] and Liao et al,[26] the relationship between multiparity and cervical cancer survival rate is statistically significant (n = 1673; p <0.0001). The reason for discrepancy between our study and other studies could be contributed to the uneven distribution of subjects in our study. At our study, 64.1% of subjects have parity ≥ 3 in a sample of only 270, while Muñoz et al conducted a multicenter study with 1673 subjects and equal distribution (53.1% were multiparity). Another factor could be the cut-off point of multiparity in our study (>3 births) are low compared to Muñoz et al, which is >5 births.

Coldman et al reported that women with a history of dysplasia, even with three consecutive negative Pap tests, evidently still have an increased risk of cervical cancer compared with women with no history of dysplasia found with Pap smear screening.[27] Mählcket alstated that the pap smear is the key in reducing the number of deaths from cervical cancer (n=6799; p=0.003).[28] In this study it was found that a history of pap smear does not provide a significant association with cervical cancer survival rate (p=0504). This could be due to fewer numbers of subjects (n=270), compared with studies of Mählck et al (n=6799).

Studies have shown that tumor size of cervical cancer affects survival rate. Smaller tumors have a better prognosis compared to larger ones.[29,30] Various publications reveal that tumor size cervical cancer stage is a prognostic factor.[21,30-33] This is in line with our results, which indicates size of mass correlates significantly to survival rate of cervical cancer (p-value<0.001).

Lymph node involvement is known to be poor prognostic factors for recurrence and survival rate in patients with cervical cancer. Lymph node involvement is also the basis for determining the schedule of adjuvant therapy in early-stage cervical cancer who received surgical therapy management.[34-36]

Locally advanced cervical cancer, which includes adenosquamous lymph node involvement post-operatively and involvement of pelvic lymph node, shown to be a poor prognostic factor as it lowers survival rate as well as increase incidence of recurrence.[37] In this study, the presence of metastasis in the pelvic lymph nodes showed no significant relationship with cervical cancer survival rate. This can be explained by the differences in the proportion of cases with pelvic lymph node involvement and without the involvement of pelvic lymph nodes (14.1% vs 85.9%).

Squamous cell carcinoma is the most common type of cervical cancer.[38-41] Prognostic significance of histologic types of cervical cancer cells is still debated. Adenocarcinoma has a worse prognostic value when compared to squamous cell carcinoma in predicting cervical cancer survival rate.[38-41] In this study, the prevalence of squamous cell carcinoma is similar to various reports on the proportion of cases of cervical cancer by histology types.[42,43] However, in this study, although the patients with squamous cell carcinoma have a lower survival rate, the relationship between the two is proven insignificant.

Keratinization is a prognostic factor in determining the survival rate of squamous cell carcinoma. In our study, there is no significant association between keratinized squamous cell carcinoma with cervical cancer survival rate (p=0.236). This is in contrast to the study by Kumar et al,[44] which revealed that keratinized squamous cell carcinoma provides a lower survival rate compared with non-keratinized squamous cell carcinoma. This difference could be explained by the number of subjects (n = 270) in our study compared to Kumar et al, as well as unbalanced ratio between subjects with keratinized and non-keratinized squamous cell carcinoma (18.7% vs 81.3%). Kumar et al,[44] reported total number of subjects was 68543, showed a balanced ratio between the two groups of subjects (45.3% vs 54.7%). According to Crissman et al[45] and Reagan et al,[46] tumor differentiation as a prognostic factor for survival rate of cervical cancer is still controversial. The data from our study showed no significant relationship found between cell differentiation to cervical cancer survival rate. (p=0.008).

## CONCLUSION

The survival rate of advanced staged cervical in the first year to fifth was 86.3%, 43.3%, 24.4%, 23.3%, 22.6% respectively and the average survival rate in our study was 22 months (SD = 4-58 months). There is no statistically significant relationship between patients and patients' husbands smoking status to advanced stage cervical cancer survival rate. Furthermore, there is no association between the patient's severity of smoking to tumor size, stage of cervical cancer, response to therapy, cell differentiation and keratinization. A bivariate analysis was done and showed that tumor size, cell differentiation, lymphovascular invasion, response to therapy, keratinization and stage of the cervical cancer has a statistically significant effect on survival rate. However, the multivariate analysis done showed that only tumor size and stage of cervical cancer had a statistically significant impact on survival rate.

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Case Series

# Pereira Suture: an Alternative Compression Suture to Treat Uterine Atony

## *Jahitan Pereira: Jahitan Kompresi Alternatif untuk Penanganan Atonia Uteri*

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## Abstract

**Objective:** To evaluate the use of Pereira suture as a conservative surgical management in postpartum hemorrhage due to uterine atony.

**Methods:** The study was performed in the Department of Obstetrics and Gynecology, Temanggung General Hospital, Central Java, Indonesia. Data was retrieved retrospectively from medical records, from January 2011 until December 2013.

**Results:** Pereira suture was done in four cases of uterine atony with failed conservative management, and the procedure was found to be successful in all cases.

**Conclusion:** Pereira suture is an alternative surgical procedure for the treatment of uterine atony after failed conservative management.

[Indones J Obstet Gynecol 2015; 3: 177-182]

**Keywords:** pereira suture, postpartum hemorrhage, uterine atony

## *Abstrak*

***Tujuan:*** *Untuk mengevaluasi penggunaan jahitan Pereira sebagai metode bedah konservatif pada kasus perdarahan pascasalin yang disebabkan oleh atonia uteri.*

***Metode:*** *Studi dilakukan di Departemen Obstetri dan Ginekologi RSUD Temanggung, Jawa Tengah, Indonesia. Data diperoleh secara retrospektif dari rekam medis, dari bulan Januari 2011 sampai Desember 2013.*

***Hasil:*** *Jahitan Pereira dikerjakan pada empat kasus atonia uteri yang gagal manajemen konservatif dan prosedur ini berhasil pada seluruh kasus.*

***Kesimpulan:*** *Jahitan Pereira merupakan prosedur bedah alternatif untuk penanganan atonia uteri yang gagal manajemen konservatif.*

*[Maj Obstet Ginekol Indones 2015; 3: 177-182]*

***Kata kunci:*** *atonia uteri, jahitan Pereira, perdarahan pascasalin*

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## INTRODUCTION

Postpartum hemorrhage (PPH) constitutes a major cause of maternal mortality, particularly in the developing world, and maternal morbidity in both developed and developing world.[1]

PPH is commonly due to the abnormalities of one or a combination of four basic processes. They are reffered to as the "4Ts' namely tone (poor uterine contractions), tissue (retained products of conception or blood clots), trauma (to the genital tract) and thrombin (coagulation abnormalities). Uterine atony is the main cause of PPH accounting for about 75-90% of all cases.[2]

The traditional management of this condition begins with conservative methods such as bimanual uterine compression, medical therapy with uterotonic agents, uterine tamponade with balloons, and occasionally arterial embolisation; the failure of which often mandates surgical intervention. Surgical measures such as ligation of the major pelvic vessels demand a rarely used skill possessed by few registrars. In the event of intractable hemorrhage despite the above measures, hysterectomy is usually the final resort.[3]

In 2005, Alcides Pereira created a new conservative surgical procedure to treat uterine atony, where a series of transverse and longitudinal sutures were

applied around the uterus and mechanically compress the uterus in an attempt to avoid peripartum hysterectomy. Pereira's original report described seven patients who underwent the Pereira technique for uterine atony, in whom conventional uterotonic agents proved to be ineffective. This technique was successful in preserving the uterus, in all seven cases, and there were no known immediate or long-term complications.[4]

Although this procedure is very effective in treating uterine atony, there are hardly any reports of this procedure being utilised in Indonesia. Our study reviews the cases in which the Pereira suture was used in Temanggung General Hospital to treat uterine atony, and their clinical outcomes are discussed.

## METHOD

The study was performed in the Department of Obstetrics and Gynecology, Temanggung General Hospital, Central Java, Indonesia. Data was retrieved retrospectively from medical records, from January 2011 until December 2013.

There were 4 cases PPH due to uterine atony, treated with Pereira suture. This procedure was performed only after uterine atony did not respond with conservative management (uterine massage, bimanual compression and the use of uterotonics, i.e. oxytocin, ergometrine and misoprostol).

The Pereira suture was originally described using multifilament absorbable Vicryl #1, but we used chromic catgut #2. Almost similar to the B-Lynch suture, before performing the Pereira suture, we carried out a test to assess the potential efficacy of this technique. The patient is placed in the Lloyd Davies or semi-lithotomy position (frog leg). An assistant intermittently swabs the vagina to determine the presence and extent of the bleeding. The uterus is then exteriorized and bimanual compression performed. If the bleeding stops on applying such compression, there is a good chance that application of the Pereira suture will succeed.

The Pereira suture consisted of a series of transverse and longitudinal sutures placed around the uterus (Figure 1 and 2).

Placement of the sutures involved a series of bites inserted superficially, taking only the serous membrane and the subserous myometrium without penetrating the uterine cavity (Figure 2). Two or three transverse circular sutures were placed first, starting in the anterior aspect of the uterus, crossing the broad ligament towards the posterior aspect of the uterus, then crossing the opposite broad ligament towards the anterior aspect and tying the suture over the anterior aspect of the uterus. The number of bites in the uterus varied according to the size of the organ. When the suture crossed the broad ligament, it was important to select an avascular area and to be sure that the fallopian tube, the uteroovarian ligament, and the round ligament were not inside the suture (Figure 1). The last transverse circular suture in the lower uterine segment served as an anchor for two or three longitudinal sutures. Each longitudinal suture started on the dorsal side of the uterus, using a knot to fix it to the lowest circular suture (Figure 3), and ended on the ventral side using another knot attached to the lowest transverse suture (Figure 4).[4]

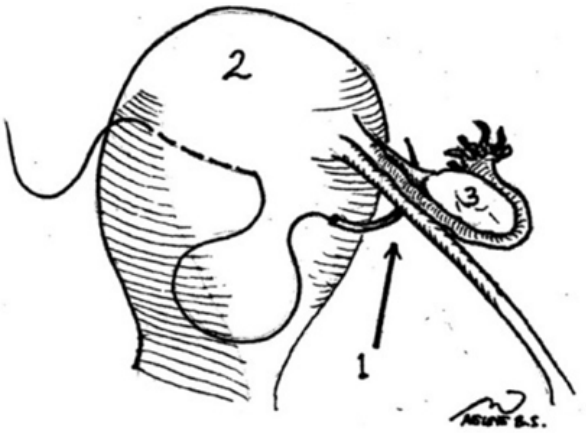


**Figure 1.** Method of applying transversal sutures. The needle is passed through avascular area of the broad ligament (1), uterus (2), ovary (3).[4]

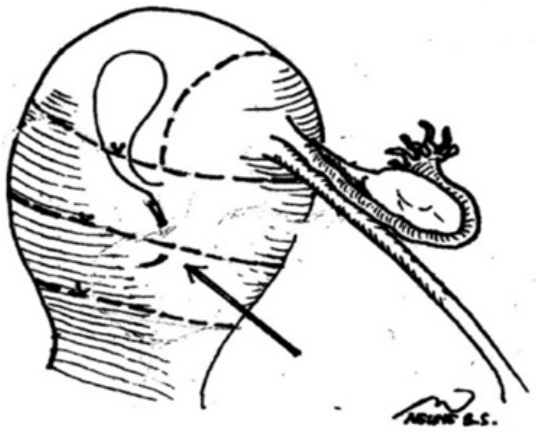

**Figure 2.** Three transverse circular sutures placed first, followed by longitudinal suture (arrow). All sutures applied with superficial intramyometrial bites.[4]

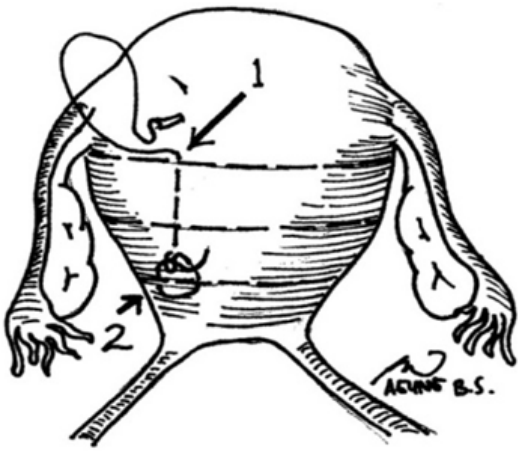


**Figure 3.** Posterior aspect of the uterus. The first longitudinal suture (1) and first knot to fix longitudinal with transversal sutures (2).[4]

**Figure 5.** Final result (anterior aspect)

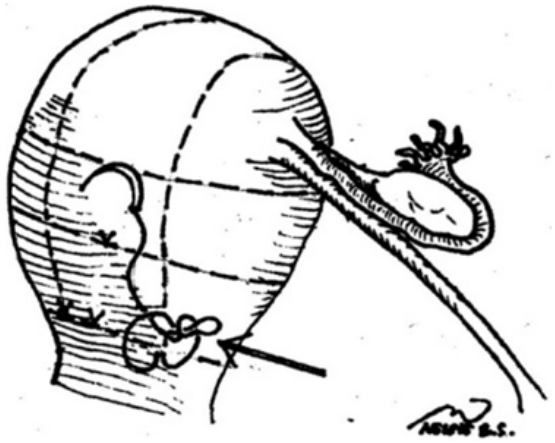

**Figure 4.** Last knot of longitudinal sutures (arrow).[4]

**Figure 6.** Final result (posterior aspect)

When each myometrial suture was placed, manual compression was applied to the uterus to achieve maximum reduction of uterine volume before tying the suture. The final result of the method is shown in Figure 5 and 6. The mean time required to complete the procedure was 5 minutes (range = 4-7 minutes).[4]

## RESULTS

The Pereira suture was attempted in 4 patients from January 2011 to December 2013. The patients' medical history, treatment, and clinical outcomes are summarized in Table 1.

Table 1. di file "tabel pereira case"

## DISCUSSION

PPH is a life threatening condition. Fortunately, medical management of PPH is quite successful, and surgical interventions are not needed in the vast majority of the cases. However, when surgical interventions are required, a procedure that is efficient and preserves fertility is preferable.[5]

In 1997, Christopher B-Lynch described an effective surgical technique to treat postpartum bleeding due to uterine atony, known as B-Lynch suture, in five women with PPH. The objective of this technique is to compress the uterus with two longitudinal sutures along its long axis without occluding the uterine arteries.[6]

Variations on this compression technique have been described by some authors, i.e. Hayman[7], Cho[8], Nelson and Birch[9], Ouahba[10], Zheng[11], Hackethal[12], Marasinghe[13], Stanojevic[14], Sulistyono et al[15], Lasso-Budiman[16], Makino-Takeda[17], Matsubara-Yano[18], Meydanli[19], Bhal[12], Malibary[12], Hwu[12], Tjalma and Jacquemyn.[12]

Although the B-Lynch technique is effective to treat uterine atony, several subsequent publications have reported its complication such as erotion and partial necrosis of the uterine wall.[20-23]

Another risk with the B-Lynch suture are the risk of infection[4] and occlusion of the uterine cavity[11] due to incision of the uterine wall and penetration of the uterine cavity with the sutures. Pereira's technique offers theoretical advantage to their technique due to the suture not penetrating the endometrial cavity, and being performed without an incision of the uterine wall, thus decreasing the risk of infection and occlusion of the uterine cavity.[4]

Alcides Pereira's original study reported 7 patients with uterine atony and actual postpartum bleeding who were successfully treated by placing compressive sutures around the uterus when conservative management was proven ineffective. The Pereira suture was successful in preserving the uterus, and hence fertility, in all 7 cases, and there were no known immediate or long-term complications.[4]

In our own series, the Pereira technique was performed in 4 women, avoiding the need for hysterectomy in all cases. Each Pereira sutures is made up of a succession of small bites of the uterus, distributing the pressure of the suture more evenly and making compression more effective. The small size of the bites applied to the uterus reduces the risk of a loop of bowel or the risk of the omentum coming between the uterus and the suture with puerperal involution. Finally, the combination of longitudinal and transverse sutures not only aids compression but also collapses the lumen of ascending branches of the uterine artery, reducing vascular flow and venous bleeding.[4]

Pereira stated that the mean time required to complete the procedure was 5 minutes (range = 4 - 7 minutes),[4] but in our report the mean time required to complete the procedure was 8.5 minutes (range = 7 - 11 minutes). This implies that we need more cases in order to complete the Pereira procedure within 5 minutes.

## CONCLUSION

Our experience implies that Pereira suture is an alternative surgical procedure for the treatment of uterine atony with failed conservative management. However, more cases are needed to achieve a faster timeframe to perform the Pereira suture.

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