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Editorial

Men's Health Infertility Management

Tono Djuwantono

Infertility is a complex and multifaceted issue that affects both men and women, requiring a comprehensive approach that considers the unique challenges and needs of each individual. Globally, infertility affects approximately 15% of the population, with male factor infertility accounting for around 50% of cases, either in isolation or in combination with female factors.[1,2] While conversations and support systems around infertility have traditionally focused on women, the role of men in this narrative is increasingly gaining recognition especially due to critical decline in sperm quality worldwide.[3,4] Global research data indicates a worldwide decline in sperm quality over the last 50 years, with a more than doubling of the decline rate since 2000. The average sperm count dropped from approximately 104 million to 49 million per millilitre from 1973 to 2019, with normal sperm counts considered to be above 40 million per millilitre.[3,5] The decline in sperm counts appears to be accelerating, with an average decrease of 1.16% per year before 2000, increasing to 2.64% per year after 2020.3,4 This trend is consistent across various regions, including South and Central America, Asia, Africa, North America, Europe and Australia.[5,6]

Accordingly, a comprehensive investigation of the male partner is essential in the assessment and management of infertile couples. Lifestyle factors could significantly impact male fertility. Smoking includes e-cigarettes, excessive alcohol consumption and exposure to high temperature water (such as from hot baths or saunas) could negatively affect sperm production and quality. Additionally, conditions like varicocele, which is an enlargement of the veins within the scrotum, could also impair sperm quality. Maintaining a healthy lifestyle, including avoiding smoking and excessive alcohol, and managing heat exposure, could help improve sperm health and overall fertility. [7]

The complexity of male infertility management underscores the need for a multidisciplinary approach, involving healthcare professionals from various specialties, including urologists, andrologists, endocrinologists and reproductive biologists. By leveraging the latest scientific evidence and technological advancements, clinicians could work collaboratively to develop personalized treatment plans which address the unique needs of each patient, ultimately improving the chances of successful conception and parenthood. Along with advancements in assisted reproductive technology, therapies are now available to address male infertility. Patients with an indication of azoospermia can undergo a microsurgical epididymal sperm aspiration (MESA) or micro testicular sperm aspiration (TESE) surgical procedure to obtain sperm from the epididymis or seminiferous tubules.[8] The sperm obtained from the TESE procedure is then frozen and could be used for pregnancy programs through in vitro fertilization (IVF).[9] Through the intracytoplasmic sperm injection (ICSI) technique, sperm with low count (oligozoospermia), reduced motility (asthenozoospermia), or even immotile sperm can be used to fertilize an egg.[10] Male cancer patients who are going to undergo a chemotherapy treatment plan may be recommended to cryopreserve their sperm before starting chemotherapy to preserve fertility.[11]

A crucial aspect of managing male infertility is preventing the decline in sperm quality. Studies have shown that increased sperm deoxyribonucleic acid (DNA) damage could be associated with a higher risk of recurrent pregnancy loss. Research suggests that sperm DNA fragmentation is more common in men from couples with recurrent miscarriages compared to fertile men. Sperm DNA integrity assays can help assess the likelihood of miscarriages, with some studies indicating that they might predict up to 39% of miscarriages. These assays measure the extent of DNA damage in sperm and can be useful in identifying potential fertility issues.[12]

Some strategies to consider include educating boys and adult men about male reproductive health, particularly encouraging a healthy lifestyle and avoiding exposure to chemicals that may harm male fertility. By increasing awareness about the prevalence and causes of male infertility, we can encourage men to prioritize their reproductive health. Healthcare providers play a pivotal role here, providing compassionate care and tailored treatment plans which address individual needs. Moreover, support networks are crucial in destigmatizing male infertility.

Semen analysis is crucial for diagnosing male infertility, but manual sperm analysis can be labor-intensive, subjective, and prone to variability. Artificial intelligence (AI) has shown promise in addressing these issues by automating sperm concentration, motility, and seminal pH assessments using microscopic optical technology. Some studies have reported a high correlation between AI-based and manual methods, while others have found discrepancies. Limitations in current AI research include small sample sizes and unclear evaluation methods, which could affect the reliability and generalizability of findings. Further research is needed to refine AI tools and validate their effectiveness in clinical settings.[13]

Ultimately, infertility is a shared journey—one that requires compassion, understanding, and collective effort. In breaking the silence surrounding men's health in infertility management, we not only empower individuals but also enrich the fabric of our society with a deeper understanding of reproductive health and resilience in the face of adversity. Together, we can redefine the narrative of infertility, embracing inclusivity and compassion every step of the way.

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Research Article

Polymorphism specific Allele Frequencies on Cervical Cancer

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Abstract

Objective: To evaluate the correlation of allele frequencies of IL-6 polymorphisms between healthy women and cervical cancer patients.

Method: The study involved gynecologists diagnosing abnormal cervical tissue in 100 women aged 17-60. Each woman provided two tissue samples: one for pap smear analysis and one for genetic research, along with a blood sample for IL-6 polymorphism analysis. Traditional polymerase chain reaction (PCR) was used for genetic analysis to confirm diagnoses. Allele-specific PCR (AS-PCR) was utilized to identify allelic polymorphisms. Pap smears identified cervical intraepithelial neoplasia (CIN) II and III, characterized by dysplastic cells and mitotic figures.

Results: The diagnostic PCR data demonstrated that 36% of participants were HPV-infected, with the greatest infection rates (50%). The AS-PCR reported that the IL-6 (rs1800795) gene detected at 174 G/C position was presented with GG, GC, and CC genotypes.

Conclusion: The result showed a significant alteration in the IL-6 (rs1800795) gene, strongly correlating with cervical cancer based on human papillomavirus infection.

Keywords: cervix cancer, human papillomavirus, interleukin-6 polymorphism, genetic analysis.

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INTRODUCTION

Papillomaviruses are a large family of viruses that can infect mammals, birds, and reptiles, and they are known to infect various species and tissues in diverse manners. One of the most common sexually transmitted infections (STIs) affecting both men and women is HPV, which infects stratified squamous epithelia. [1] HPV can cause warts and other benign proliferative lesions, with a smaller subset of viruses capable of inducing premalignant and malignant abnormalities. The vaginal area is particularly susceptible to the development of malignant diseases, the most prevalent being cervical cancer.[2]

The initiation of viral genome replication defines the early and late stages of the HPV life cycle, respectively. Additionally, epithelial cell differentiation correlates with the transition from early to late stages in the HPV life cycle. The initial stages involve tropism and entry. Receptor-mediated endocytosis allows HPV virus particles to enter cells after attachment to the extracellular matrix and binding to heparan sulfate proteoglycan receptors.[3] Once inside the cytoplasm, the virus's capsid becomes embedded in endosomes. Acidification of the endosomes (low pH) triggers the release of the L2 capsid protein and subsequent rupture of the endosomal membranes.[4] Each phase of viral genome replication—establishment, maintenance, and amplification—is intricately linked to specific levels of cell differentiation.[5,6].

Human papillomavirus (HPV) is a sexually transmitted virus that primarily affects females but can also infect males. There are over a hundred different types of HPV, but only high-risk (HR-HPV) types are associated with the

progression of cervical intraepithelial neoplasia (CIN) to cancer. However, there are also other types of HPV that cause genital warts, known as low-risk types. HPV-16 infections are responsible for 85-95% of cervical cancer cases. [7-9]

The cytokine interleukin-6 (IL-6) may have a role in the development of cervical cancer. Cervical cancer growth is stimulated by IL-6 through vascular endothelial growth factor (VEGF)-dependent angiogenesis mediated by the signal transducer and activator of transcription 3 (STAT3) pathway.[10,11] Single-nucleotide polymorphisms (SNPs) are only one example of the many potential influences on gene expression. [12, 13] This study aimed to analyze the distribution of allele frequencies of IL-6 polymorphisms in both healthy women and patients with cervical cancer attributed to human papillomavirus (HPV).

METHODS

Patients and samples

The present research used a cross-sectional design and collected data from participants between January 2022 and 2023 to identify HPV, and a case-control study design to identify IL-6 polymorphisms. In this study, gynecologists at Al-Diwaniyah Hospital for Women and Children's Cervix Department and at private clinics in Al-Diwaniyah City, Iraq, detected cervical tissue anomalies in 100 women aged 17 to 60 years old. Women who met the study's criteria were approached for participation and given the opportunity to provide informed permission. Patients' names, ages, menstrual cycles, pregnancies, surgical procedures (hysterectomy, cone biopsy, oophorectomy), treatments (hormonal, radiation, or chemotherapy), and histories of abnormal cervical cytology and other conditions were documented.

Samples were collected from women with normal menstrual cycles during the mid-cycle phase. However, samples from other women were collected at various stages of their menstrual cycles. Participants were instructed to refrain from using tampons, vaginal foams, jellies, or any vaginal creams or medications before sampling. Sampling was not allowed within 48 hours after intercourse. Specimens were collected following protocols established by a pathologist or trained technician, using a sterile, single-use bivalve speculum. Each participant provided two tissue samples: one for pap smear analysis and genetic research, and blood samples were taken for IL-6 polymorphism detection.

Samples were taken from the transformation zone (ecto-endocervical junction) using a thin prep cytobrush that rotated a full 360 degrees for the Papanicolaou technique. The Cytobrushes were quickly placed into methanol-containing ThinPrep transport medium vials.

Pap Smear Test

Pap staining was used to prepare the samples for microscopy, and the slides were put under a microscope [14, 15]. Bethesda criteria were used for the cytological abnormality reporting [14,16, 17].

Molecular Techniques
Extraction of viral DNA

The viral DNA extraction was performed using a G-spinTM Total DNA Extraction Kit (iNtRON, Korea), following the manufacturer's recommended Body fluid protocol. The quantity and quality of the extracted DNA were assessed using a NanoDrop reader. The extracted DNA was stored frozen at -20 degrees Celsius for future use.

Extraction of Human Genomic DNA

The genomic DNA extraction from blood specimens was conducted using the gSYAN DNA Extraction Kit (Geneaid, USA), following the Frozen Blood protocol provided with the kit. The quantity and integrity of the extracted DNA were assessed using a NanoDrop spectrophotometer.

Diagnostic PCR

The primary capsid protein L1 gene served as a molecular marker in the PCR, conducted using the Maxime PCR PreMix Kit (iNtRON, Korea).[18] A total of 20 µl of PCR solution was prepared, comprising 5 µl of DNA (5-50 ng), 1 µl each of forward and reverse primers for the L1 gene (10 pmol/ each), and 13 µl of PCR-grade water. Additional components included DNA polymerase, dNTPs, and MgCl2 in the PCR reaction mixture. The thermocycler was programmed as follows: initial denaturation at 95ºC for 5 mins (1 cycle), followed by denaturation at 95ºC for 30s, annealing at 58ºC for 30s, and extension at 72ºC for 60s for 35 cycles, with a final extension step at 72ºC for 5 mins (1 cycle). The PCR products were analyzed

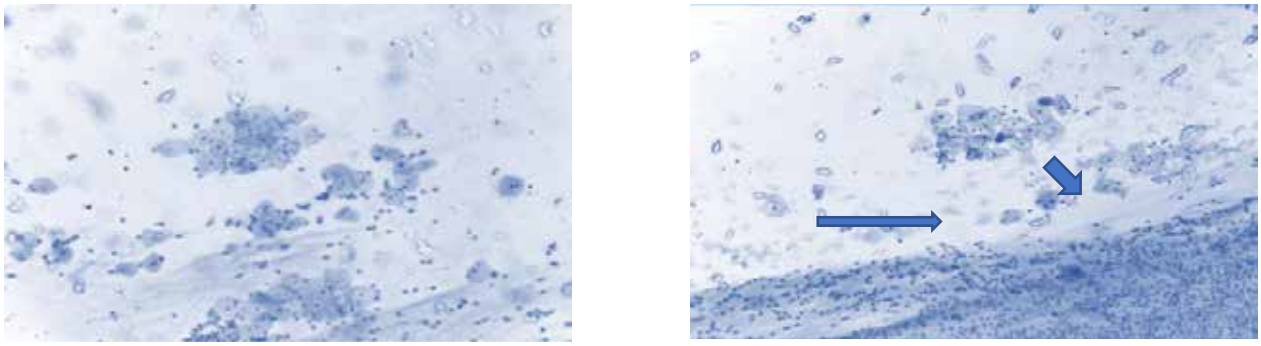
by agarose gel electrophoresis, and the bands were visualized under a UV transilluminator.

PCR of Allele Polymorphism

Patients with HPV infection and healthy controls were subjected to an AS-PCR technique to identify and genotype the IL-6 -174G>C (rs1800795) gene polymorphism. The procedure followed the outline given [8,19]. We used a (GoTaq® G2 Green Master Mix kit) to make the AS master mix, and then used this mix to run two separate reactions on each sample, as recommended by the manufacturer. Each reaction (25µl), 5µl DNA, 2µl (10pmol) for each direction of the primers; forward (wild type or mutant) and common reverse, 12.5µl G2 Green master mix, and 3.5µl PCR water, were utilized. A thermocycler was employed at; (95ºC for 5mins for one-cycle)-initial denaturation, (95ºC for 30s, 55ºC for 30s, and 72ºC for 30s) for 35 cycles of denaturation, annealing, and extension, respectively, and (72ºC for 5mins for one cycle) final extension. An electrophoresis using a 2% Agarose gel was followed with PCR products visualized using a UV-light based screener.

RESULTS

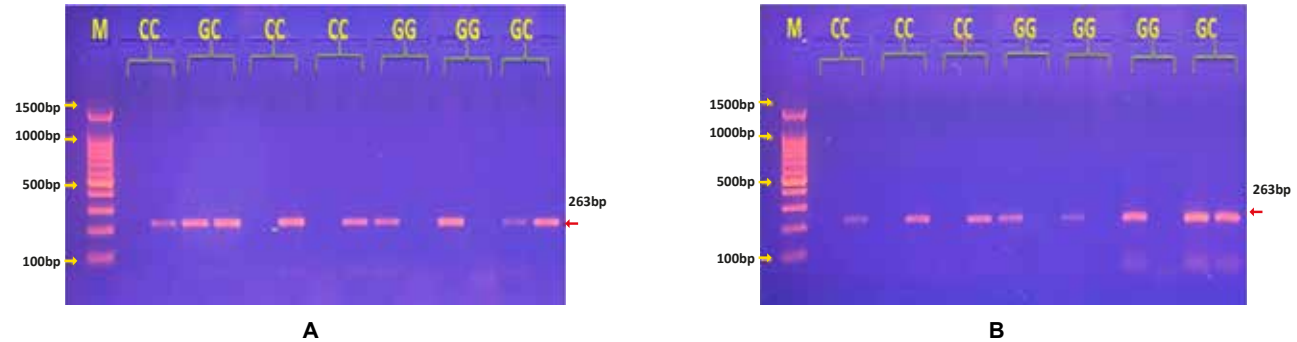
The pap smears revealed cervical intraepithelial neoplasia (CIN); II and III, in which dysplastic cells and mitotic figures were detected (Figure 1).



A B

Figure 1. Cervical intraepithelial neoplasia (CIN). A. CIN II (HSIL). B. CIN III (HSIL). It shows dysplastic cell, mitotic figures (blue arrow). Giemsa stain (X10).

The AS-PCR reported that the IL-6 (rs1800795) gene detected at 174 G/C position was presented with GG, GC, and CC genotypes (Figure 2 and tables 1-4).



A B

Figure 2. Images of agarose gel electrophoresis. It displays IL-6 -174G>C (rs1800795) gene polymorphism in A. HPV-patient and B. Healthy samples. Where M: a (1500-100bp) ladder. The GG: wild (G) homozygote allele, CC: mutant (C) allele, and GC): heterozygote (G and C) allele.

Table 1. Genotypes of IL-6 G/C 174 in Cervical Dysplasia without HPV Women and Healthy Controls

Genotype	G1 No.=50	G2 No.=64	G1 vs G2				
			X^2	*P-value*	OR	Etiological fraction	95% CI
GG	38	32	8.01	0.005*	0.31	0.29	0.1400-0.7122
GC	8	18	2.34	0.126	2.05	0.13	0.8089-5.2171
CC	4	14	4.06	0.044*	3.22	0.1	0.9883-10.4913

Table 2. Genotypes of IL-6 G/C 174 in healthy controls and HPV infected women

Genotype	G1 No.=50	G3 No.=36	G1 vs G3				
			X^2	*P-value*	OR	Etiological fraction	95% CI
GG	38	16	8.92	0.003*	0.25	0.3	0.1003-0.6363
GC	8	10	1.75	0.185	2.01	0.12	0.7062-5.7732
CC	4	10	6.01	0.014*	4.42	0.1	1.2605-15.5204
Allele							
G	84	42	0.4	0.52	0.83	0.29	0.4561-1.4947
C	16	30	0.4	0.52	1.21	0.21	0.6690-2.1927

G1: Negative healthy control; G2: cervical dysplasia without HPV

Table 3. IL-6 G/C 174 allele frequency distribution in healthy control and HPV infected women

Allele	G1 No.=50	G3 No.=36	G1 vs G3				
			X^2	*P-value*	OR	Etiological fraction	95% CI
G	84	42	0.4	0.52	0.83	0.29	0.4561-1.4947
C	16	30	0.4	0.52	1.21	0.21	0.6690-2.1927
Genotype	**G2 No.=64**	**G3 No.=36**	**G2 vs G3**				
			X^2	*P-value*	OR	Etiological fraction	95% CI
GG	32	16	0.28	0.59	0.8	0.24	0.3524-1.8163
GC	18	10	0	0.97	0.98	0.16	0.3955-2.4429
CC	14	10	0.44	0.51	1.37	0.14	0.5367-3.5156

G1: Negative healthy control; G3: Patients with HPV

Table 4. IL-6 G/C 174 allele frequency distribution in HPV infected women and cervical dysplasia without HPV

Allele	G2 No.=64	G3 No.=36	G1 vs G3				
			X^2	*P-value*	OR	Etiological fraction	95% CI
G	78	42	14.08	0*	0.27	0.33	0.1310-0.5429
C	46	30	14.08	0*	3.75	0.15	1.8420-7.6342

G2: cervical dysplasia without HPV; G3: Patients with HPV

DISCUSSION

The current study demonstrated a notable association between IL-6 polymorphisms and high-risk HPV as predictors of cervical cancer incidence in women. This observation is consistent[20], with prior research which documented a significantly higher prevalence of the IL-6-174 GG genotype [OR=3.9; P=0.001]. Moreover, individuals with GG and GC genotypes exhibited elevated IL-6 levels in their serum. Furthermore, untreated patients showed a considerably higher prevalence of IL-6 compared to treated cases.

In another study, the prevalence of the CC genotype was 20.3% among cancer patients and 15.1% among healthy volunteers[21, 22]. A similar study conducted in China reported a lower prevalence among patients (9.4%) compared to controls (4.4%). A meta-analysis suggested that the risk of cervical cancer is associated with the C allele at the -174 G/C locus[23]. Researchers further indicated that individuals with GC+CC genotypes (57.1% in patient cases vs. 41.5% in healthy controls) are at increased risk of cervical cancer. The absence of the CC genotype among cancer cases and its presence in only 1.2% of healthy controls highlights the potential risk of

this cancer in the Brazilian community[24].

The incidence of the GC+CC genotype ranged from 22.5% in group I to 26.4% in group II and peaked at 53.4% in group III. The CC genotype was detected in approximately 2.3% to 3.1% of their respective populations. Similar patterns were observed among South Indian and West Gujarati populations, where the CC genotype frequencies were 2.9% and 1.7%, respectively. Studies conducted in various North Indian communities reported varying frequencies ranging from 0.2% to 6.0% to 6.5%. These findings underscore the relatively low prevalence of the CC allele among Indians, a trend also noted in Gujarati Indians residing in Houston, Texas.[25].

CONCLUSION

The current study highlights a significantly altered IL-6 (rs1800795) gene strongly associated with human papillomavirus (HPV) infection-related cervical cancer in the Iraqi population. Therefore, further investigations into this gene across different regions are crucial for establishing it as a diagnostic marker for papillomaviruses. Additionally, comprehensive genetic studies are recommended to validate these findings and explore their broader implications.

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Research Article

The Antibiotic Prescribing Practices of Gynecologists in Abdominal Hysterectomy

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Abstract

Objective: To evaluate the pattern of antibiotics used for abdominal hysterectomy by gynecologists in infected and non-infected cases.

Methods: Data was collected through an online survey of gynecologists in Surabaya, Indonesia.

Results: A total of 200 gynecologists were involved in this study. All of them used prophylactic antibiotics in all cases of abdominal hysterectomy, and the most commonly used was cefazoline (70.5%), followed by ceftriaxone (15.5%) and cefotaxime (9%). Most gynecologists (68%) gave 2 grams of prophylactic antibiotic, and 79,5% of antibiotics were administered within 30 minutes before surgery. Additional antibiotics during surgery were given in prolonged surgery (79.01%) and intraoperative bleeding > 1500 mL (48.14%). The most common additional dosage used was 1 gram (72.9%), and most gynecologists (37.2%) continued antibiotics for one day ahead. The type of therapeutic antibiotics used for infected cases was varied, consisting of ceftriaxone (50.5%), metronidazole (42%), cefotaxime (17%), cefazoline (15.5%), gentamicin (12%), ampicillin-sulbactam (4%), and amoxicillin-clavulanic acid (3.5%). Most gynecologists (43.7%) gave these antibiotics for three days.

Conclusion: The majority of gynecologists in Surabaya already use prophylactic antibiotics for abdominal hysterectomy and therapeutic antibiotics for infected cases following the existing guidelines

Keywords: antibiotics, gynecologist, hysterectomy, infection.

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INTRODUCTION

Hysterectomy has become the second most commonly performed surgical procedure for reproductive-age women and is widely used for treating various gynecologic problems. In the United States, 90% of hysterectomy procedures are performed for benign gynecological reasons such as fibroid, abnormal uterine bleeding, endometriosis, and uterine prolapse[1]. The hysterectomy rate in the United States is relatively high: 510 per 100.000 women[2], while in some European countries like Denmark, the incidence is generally lower, as low as 173 per 100.000 women[3]. Hysterectomy rates in Asian countries are lower, ranging from 1.7-9.8% of all women in India, Yordania, and El Salvador[4].

The prophylactic antibiotic is strongly suggested in gynecology surgery[5–10]. The prophylactic antibiotic has been shown to reduce maternal morbidity, healthcare costs, and antibiotic use[11,12]. Prophylactic antibiotics also help prevent postoperative and surgical wound infections[5,10,13–16].

According to the Scottish Intercollegiate Guidelines Network's 2014 guidelines on surgical antibiotic prophylaxis, these antibiotics must be used appropriately, backed up by evidence

of efficacy, and their effect on the patient's normal bacterial flora and immune system must be minimized[17]. Several meta-analysis studies suggest that prophylactic antibiotics (of various types, durations, and routes) effectively reduced the risk of severe infection following surgery, including abdominal hysterectomy[18–22].

Antibiotic misuse can result in serious health consequences, mainly antibiotic resistance[23–27]. Bacteria, viruses, fungi, and parasites can acquire antibiotic resistance, lowering their efficacy[26–28]. Antibiotic resistance affects around 2.8 million individuals in the United States, and over 35,000 people die yearly due to antibiotic resistance[29]. Antibiotic resistance develops when bacteria and fungi acquire the ability to resist medications that are intended to kill them. As a result of the bacteria surviving and growing, physicians must be cautious about this happening. As a result, antibiotics must be provided appropriately and at the appropriate time to avoid infection[30]. Regarding drug selection and administration timing, dose, and duration, inappropriate antibiotic use is a critical factor in the emergence of antibiotic resistance.

Although recommendations for antibiotic use have been established, in practice, antibiotic use in abdominal hysterectomy varies according to the attending doctor's discretion. Along with adherence to rules, gynecologists' personal experiences influence how antibiotics are administered for hysterectomy surgery. There is a wide variation in the prophylactic antibiotic use, antibiotic type selection, administration timing, and the addition of antibiotics during and after surgery in the hospital setting. This study aimed to identify the type, dosage, timing of administration, reasons, dan duration of antibiotic use for abdominal hysterectomy in infected and non-infected cases performed by gynecologists in Surabaya, Indonesia's second-largest city. This study is important to determine the characteristics of antibiotic use in infected and non-infected cases by gynecologist.

METHODS

This study was conducted in Surabaya, Indonesia, from July to August 2021. All Gynecologists from hospitals were included in the study. Ethical clearance was approved by the Ethical Committee of Universitas Airlangga Hospital No. 138/KEP/2021), Surabaya, Indonesia. The research participants were gynecologists working in all hospitals in Surabaya based on the inclusion and exclusion criteria (total sampling size). Gynecologists still performing a hysterectomy in treating gynecologic cases meet the inclusion criteria. Participants are automatically excluded if they choose not to respond to the survey.

The study aims to evaluate the pattern of antibiotic use for abdominal hysterectomy in infected and non-infected cases. Infected cases were defined as any infection in the mother that occurred during surgery, including systemic or local (reproductive tract infections). We excluded any hysterectomy performed for malignancy indication. Non-infected cases were benign gynecological cases requiring abdominal hysterectomies, such as uterine fibroid and ovarian cysts. The primary outcome of this study was the pattern of antibiotic use, including prophylactic antibiotic use, antibiotic type selection, administration timing, and the addition of antibiotics during and after surgery.

Based on the respondents' age, work history, and place of employment, the clinical characteristics of each were evaluated. The medical facility is separated into primary, secondary, tertiary, and exceptional hospitals for mothers and child. The completeness of the range of medical services that can be offered, the number of beds, the kind of medical services (specialist or subspecialist), and the availability of medical staff are the factors that differentiate types of hospitals. Electronic form were used to conduct online interviews that provided the research data. Then, the research team made contact with potential study participanst, informed them about the study, and got their informed consent. Following their completion of the questionnaire, study participants provided the research with the data. The information was shown as descriptive statistcs.

RESULTS

Two hundred gynecologists agreed to participate in this study (50% response rate of the population). Due to the pandemic, the remaining gynecologists did not respond. Most participants were aged 30–60 (93.5%) and had less than ten years of work experience (53.5%). Participants worked in various types of hospitals, with the majority in secondary (39%) and primary hospitals (33%) (Table 1).

Table 1. Characteristics of Participant

Characteristics	N (%)
Ages (years old)	
30 – 39	67 (33.5)
40 – 49	65 (32.5)
50 – 59	55 (27.5)
60 – 69	11 (5.5)
70 - 79	2 (1)
Working Experience (years)	
>20	14 (7)
10 – 20	79 (39.5)
< 10	107 (53.5)
Hospital Type	
Tertiary care hospital	30 (15)
Secondary care hospital	78 (39)
Primary care hospital	66 (33)
Mother and Child hospital	24 (12)
Others	2 (1)

Table 2 shows the pattern of antibiotics used for abdominal hysterectomy in non-infected gynecology cases. All gynecologists used prophylactic antibiotics in these cases. The type of antibiotics used were varied, but the most commonly used were cefazoline (70.5%), ceftriaxone (15.5%), and cefotaxime (9%). The most used dosage of prophylactic (iv) antibiotic was 2000 mg (68%), with the majority administered 30 minutes before surgery (79.5%). During surgery, interestingly, 2.5% of the patients received additional iv antibiotics routinely, whereas 40.5% received additional antibiotics based on specific situations such as prolonged operation (79%), bleeding > 1.5 Liters (48.1%), and cases with a risk of infection (27.2%). Even though in non-infected cases, 28.5% of the participants continued IV antibiotics after surgery for the most common one day (37.2%). The most common antibiotics iv used after surgery were cefazoline (43%), ceftriaxone (30.2%), and metronidazole (15.1%). In addition, several gynecologists continued to give antibiotics orally (35%). Cefadroxil and ciprofloxacin were the most common oral antibiotics after surgery and the most common oral antibiotics for five days (64.2%) (Table 2).

Table 2. Antibiotics Used in Non-Infected Abdominal Hysterectomy Surgery

Antibiotics Use Profile	N (%)
Prophylactic antibiotic use	
Yes	200 (100)
No	0
Type of prophylactic antibiotic Used (iv)	
Cefazoline	141 (70.5)
Ceftriaxone	31 (15.5)
Cefotaxime	18 (9)
Cefoperazone	2 (1)
Cefuroxime	5 (2.5)
Amoxicillin Clavulanic Acid	4 (2)
Ampicillin Sulbactam	3 (1.5)
Gentamycin	3 (1.5)
Phosphomycin	1 (0.5)
Antibiotic dosage (mg)	
500	1 (0.5)
1000	51 (25.5)
1000-2000	9 (4.5)
2000	136 (68)
2000-3000	2 (1.1)
Timing of antibiotic administration	
>30 minutes before surgery	36 (18)
<30 minutes before surgery	159 (79.5)
After abdominal incision	5 (2.5)
Addition of antibiotics during surgery	
Yes	5 (2.5)
No	114 (57)
Depend on condition	81 (40.5)
What condition necessitates the addition of antibiotic	
Prolong surgery	64 (79)
Bleeding > 1.5 L	39 (48.1)
Infection risk	22 (27.2)
Others	6 (7.4)
Antibiotics (iv) continued after surgery	
Yes	57 (28.5)
No	143 (71.5)
Type of Antibiotics (iv)	
Cefazolin	37 (43)
Cefotaxime	8 (9.3)
Ceftriaxone	26 (30.2)
Metronidazole	13 (15.1)
Ampicillin Sulbactam	3 (3.5)
Amoxicillin Sulbactam	2 (2.3)
Cefuroxime	3 (3.5)
Gentamycin	2 (2.3)
Duration of antibiotics (iv) continued after surgery (days)	
1	32 (37.2)
2	11 (12.8)
3	21 (24.4)
5	10 (11.6)
7	1 (1.2)
Antibiotics oral continued after surgery without infection risk or complications	
Yes	70 (35)
No	130 (65)
Type of oral antibiotics given after surgery	
Cefadroxil	36 (51.4)
Ciprofloxacin	12 (17.1)
Amoxicillin	13 (18.6)
Cefixime	6 (8.6)
Azithromycin	1 (1.4)
Amoxicillin Clavulanic Acid	3 (4.3)
Levofloxacine	1 (1.4)
Duration of oral antibiotics continued after surgery (days)	
2	1 (1.4)
3	3 (22.8)
4	1 (1.4)
5	45 (64.2)
7	7 (10)

We also evaluated antibiotics used for hysterectomy in infected gynecology cases. Every patient received therapeutic antibiotics before and after surgery, except for 4% of gynecologists who did not continue giving antibiotics. The type of antibiotics commonly used were ceftriaxone (51.6%), metronidazole 50%), cefotaxime (14.1%), Gentamycin (12.5%), Amoxicillin clavulanic acid (9.9%) and Ampicillin Sulbactam (6.3%). These antibiotics can be used as a single regimen or combined with two or more drugs. Most gynecologists administered therapeutic antibiotics (iv) for three days (43.7%) and five days (32.3%). Reference of their prophylactic and therapeutic antibiotic use was from their operational hospital guidelines (46.5%) as the most commonly used, followed by guidelines given when they were obstetric gynecology trainees (18.5%) (Table 3).

Table 3. Antibiotics Used in Infected Abdominal Hysterectomy Surgery

Infected Cases Surgery	n %
Type of Antibiotics (iv)	
Ceftriaxone	101 (50.5)
Cefazoline	31 (15.5)
Cefotaxime	34 (17)
Metronidazole	84 (42)
Meropenem	2 (1)
Amoxicillin Clavulanic Acid	7 (3.5)
Ampicillin Sulbactam	8 (4)
Cefuroxime	1 (0.5)
Gentamicin	24 (12)
Amikacin	2 (1)
Antibiotics continued after surgery	
Yes	192 (96)
No	8 (4)
Type of antibiotics administrated after surgery	
Cefriaxone	99 (51.6)
Metronidazole	96 (50)
Cefazoline	5 (2.6)
Amoxicillin Clavulanic acid	19 (9.9)
Cefotaxime	27 (14.1)
Gentamycin	24 (12.5)
Ampicillin Sulbactam	12 (6.3)
Cefadroxil	2 (1)
Amikacin	1 (0.5)
Cefuroxime	1 (0.5)
Meropenem	1 (0.5)
Ciprofloxacine	1 (0.5)
Duration of antibiotics administrated after surgery (days)	
1	14 (7.3)
2	2 (9.4)
3	84 (43.7)
4	3 (1.6)
5	62 (32.3)
7	7 (3.6)
14	1 (0.5)
Until normal temperature	1 (0.5)
Consideration of Antibiotics choices	
Based on the protocol in the specialist program	37 (18.5)
Based on the protocol in the hospital where the doctors work	93 (46.5)
Based on the recent seminar attended	19 (9.5)
Based on the recent evidence from a medical journal	33 (16.5)
Others	18 (9)

DISCUSSION

This study showed that all gynecologists administered prophylactic antibiotics for hysterectomy. This is the following recommendation that all women who will have a hysterectomy procedure should receive prophylactic antibiotics[21,31–34]. Prophylactic antibiotics aim to lower antimicrobial colonization pressure to a level where the women's immune system can overcome it when surgery is performed[35]. Prophylactic antibiotics have been shown to minimize the incidence of all types of infection following surgery, including abdominal wound infection, urinary tract infection, pelvic infection, and fever[21].

The Cephalosporine group was this study's most commonly utilized antibiotics (cefazoline, ceftriaxone, and cefotaxime). First-generation cephalosporine is the first drug of choice as a prophylactic antibiotic for hysterectomy, according to the Society of Obstetricians and Gynecologists of Canada (SOGC) and American College of Obstetrician and Gynecology (ACOG). If the patient is allergic to cephalosporin, an alternate regimen such as clindamycin, erythromycin, or metronidazole might be used instead[31,33]. Because of its broad antibacterial spectrum (most gram-positive and harmful bacteria) and low incidence of allergies and adverse events, cephalosporine has become the preferred prophylactic antibiotic for most surgical procedures[32,36].

Most antibiotics were given before surgery (less or more than 30 minutes). This method corresponds with the SOGC's recommendation that antibiotics be administered 15-60 minutes before skin incision[31]. The timing of antibiotic administration should be adjusted to the antibiotic type, such as fluoroquinolone and vancomycin, which should be infused over a prolonged period (>60 minutes) before incision to avoid drug toxicity[37]. However, using other antibiotics increases the risk of surgical site infections in parallel with the time between the drug administration and the skin incision[38].

Fifty percent of postoperative febrile morbidity was suffered by patients who did not receive prophylactic antibiotics[39].

2.5% of gynecologists routinely used prophylactic antibiotics after abdominal incisions, contrary to current recommendations. This routine was ineffective in preventing infection after hysterectomy because intraoperative antibiotics were inadequate to reduce microbial burden in the incision site during surgery[21,31,32,34,37,38]. This finding suggests that a minority of our study participants did not comply with the updated prophylactic antibiotics protocol guidelines. Most additional antibiotics within surgery after the prophylactic antibiotic was administered for specific cases like prolonged surgery (1-2 times the drug's half-life) and massive bleeding (blood loss> 1500 mL). If cefazoline is used, an extra dose should be given if the surgery lasts more than 3 hours[21,31,32,34,37].

Inappropriate use of antibiotics was also found after surgery. 28.5% of participants were given antibiotics routinely after surgery, respectively, without appropriate justification (infection). Antibiotics after surgery are generally administered orally. Following surgery, oral antibiotics such as cephalosporin, fluoroquinolones, and penicillin are commonly used. Prophylactic antibiotics should not be continued after surgery unless there is a medical indication. Patients given additional antibiotics during surgery should stop administration within 24 hours of the procedure[34,39,40]. Continued antibiotics after surgery are not increasing the effectiveness of preventing surgical site infection. On the other hand, administering prophylactic antibiotics in a single dosage can save up to 75-80% of the cost[41]. Even a study revealed that prolonging antibiotics more than 24 hours after surgery increases the risk of surgical site infection both in the hospital and after discharge[42].

The pattern of antibiotics used in infected gynecology cases is more varied, defined by the type of infection. The therapeutic antibiotic is often given before surgery, so prophylactic antibiotics are unnecessary. Broad-spectrum antibiotics such as ceftriaxone, metronidazole, and cefotaxime are the most commonly used. Furthermore, second-line antibiotics are also used in infected cases, such as amoxicillin-clavulanic acid, ampicillin-sulbactam, cefuroxime, amikacin, and meropenem. After surgery, 96% of therapeutic antibiotics are continued, but some are replaced with different types based on the results of blood or tissue cultures and antibiotic sensitivity tests.

Most of the prophylactic and therapeutic antibiotics chosen by gynecologists are based on their working hospital protocols and antibiotic guidelines, which were given when they were still obstetrics and gynecology trainee. A few gynecologists have updated their knowledge about antibiotic use based on the latest evidence-based from scientific journals.

The prophylactic antibiotic must be administered before incision to minimize incision site and postoperative infection. Antibiotics can be continued if there is an indication. The therapeutic antibiotic type is given based on the specific type of infection. To standardize the use of antibiotics by all gynecologists for hysterectomy surgery, the hospital must periodically update and socialize the appropriate established antibiotics protocol.

Limitation of this study is the study design by online questionnaire. The fact that the case details were not examined may also have an impact on the antibiotics chosen by gynecologist. Additionally, just one major Indonesian city's gynecologist were included in this study.

CONCLUSION

Most gynecologists have already employed prophylactic antibiotics for hysterectomies according to the guidelines.This study concluded that all gynecologist in Surabaya has provided prophylactic antibiotic in accordance with recommendations for hysterectomy procedurs. Continued medical education update is required to keep up withfollow the recent guidelines, especially in antibiotics use. Moreover, establishing an antibiotics protocol in the hospital can reduce the risk of inappropriate antibiotics used by medical personnel. More trials with a prospective cohort design should be conducted to verify this preliminary findings.

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Research Article

Multidisciplinary Approach of Placenta Accreta Spectrum Management to Reduce Blood Loss and Prevent Organ Injury in Referral Center

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Abstract

Objective: To investigate the differences in blood loss and organ injury at our PAS referral center over the past six years.

Methods: This retrospective analytical study included 150 subjects diagnosed with PAS based on histopathological findings from 2018 to 2023 at the PAS Center of Dr. Moewardi Regional Hospital, Surakarta, Indonesia. Subjects were divided into two groups: before 2020 and after 2021, based on multidisciplinary team appointments.

Results: The highest number of Placenta Accreta Spectrum (PAS) cases occurred in 2020, with 36 patients. Hysterectomy was the most frequently performed procedure for managing PAS in all groups. However, differences in blood loss, organ injury, and length of hospital stay between the periods from 2018 to 2020 and 2021 to 2023 were statistically significant ($p < 0.05$).

Conclusion: Multidisciplinary approaches involving various medical specialties and teams are essential to ensure maternal safety and effectively manage massive blood loss and organ damage during PAS surgery procedures.

Keywords: Placenta accreta spectrum, Blood loss reduction, Organ injury prevention.

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INTRODUCTION

Placenta Accreta Spectrum (PAS) is one of the most dangerous pregnancy complications, significantly associated with maternal morbidity and mortality[1]. In Indonesia, the incidence of Placenta Accreta Spectrum (PAS) was 2% in 2016 and increased to 4% by 2018. This trend correlates with the growing prevalence of pregnancies occurring after previous uterine surgeries observed over the past three decades.[2].

PAS can lead to severe postpartum hemorrhage (PPH) and a mortality rate of up to 30% when prenatal diagnosis and surgical decisions are suboptimal.[3]. This high mortality is attributed to the challenges in separating blood vessels from the abnormal insertion site.[4]. From 2015 to 2020, hemorrhage was the leading cause of death in pregnant women with PAS globally, accounting for approximately 88.5% of all placenta accreta cases.[5].

The surgical procedure of the PAS typically requires difficult pelvic dissection in areas with anatomic distortion and extensive aberrant neovascularization[6]. In numerous cases, clinicians encounter an unexpected intraoperative condition of PAS, which can pose potentially life-threatening risks. Additionally, the bladder and ureters are the organs most commonly damaged during such surgeries. Therefore, surgeons must employ a systematic and strategic approach to enhance prevention of urologic injuries.[7].

Numerous studies have explored PAS, but only a few publications compare complications before and after the implementation of multidisciplinary approaches in PAS centers. Multidisciplinary collaboration can effectively mitigate massive hemorrhage and minimize potential organ injury

during the management of PAS. Furthermore, involving expert personnel and identifying critical steps in developing improvement plans can facilitate better management of at-risk patients in the future, leading to improved outcomes. This study investigated the difference in blood loss and organ injury between two groups before and after 2020 (2018 - 2023) in our hospital.

METHODS

This retrospective analytic study included subjects diagnosed with PAS based on histopathological findings. Data were collected from 2018 to 2023 at the PAS Center of Dr. Moewardi Regional Hospital in Surakarta, Indonesia. A total of 150 subjects were divided into two groups: Group 1, before the establishment of multidisciplinary teams in late 2018, and Group 2, from 2021 to the present, after the team's formation.

According to the PAS center criteria, our hospital has multidisciplinary expertise and experience, encompassing maternal-fetal medicine, gynecologic oncology, vascular and trauma surgery, urologic surgery, intensivists, neonatologists, interventional radiologists, anesthesiologists, and specialized nursing staff.[8]. Therefore, all divisions involved from initial until post-operative procedure management.

The bleeding complications and injury to surrounding organs were assessed during the surgery and then recorded in the medical record as an operative report for evaluation. In addition, discussion after the multidisciplinary surgery was conducted to improve the operative technique to reduce complications in future cases. This is because placenta accreta may continue to exist in line with the increase in Cesarean Section (CS) cases as one of the risk factors.

RESULTS

A total of 150 subjects were collected. The characteristics of the subjects are presented in Table 1. There were 75 subjects in group 1 before integrated team was set up (2018-2020) with highest number of cases in 2020. The age of the subjects ranged from 23 - 45 years old, and the average in the third decade.

Table 1. Characteristics of the Total Subject within the Past Six Year

	Year	Cases	Maternal Age (year)
before Multidisciplinary (n)[a]	2018	8	35 (30 – 40)[b]
	2019	31	34 (23 – 45)[b]
	2020	36	36 (30 – 44)[b]
after Multidisciplinary (n)[a]	2021	26	36 (30 – 41)[b]
	2022	34	35 (23 – 43)[b]
	2023	15	32 (24 – 44)[b]

Annotation:[a]Amount of the cases per year; [b]Mean (Interquartile range)

PAS is divided into three categories: accreta, percreta, increta. The study showed percreta increased steadily over six years. The highest rate was in 2022 with 22 cases(64.7%) followed by accreta , only 12 cases from the total 34 cases (Table 2). Hysterectomy became the most favorable procedure for managing PAS before 2020, with highest number in 2019. Conservative method became more popular in 2023 performed 66.7% of total cases.

Table 2. Characteristics of the Histopathological Findings and Surgery Procedure

	Year					
	2018	2019	2020	2021	2022	2023
Histopathology, n (%)[a]						
Accreta	8 (100)	27 (87.0)	14 (38.9)	6 (23.0)	12 (35.2)	9 (60.0)
Increta	0	2 (6.5)	1 (2.8)	1 (3.8)	0	1 (6.7)
Percreta	0	2 (6.5)	21 (41.7)	19 (73.0)	22 (64.7)	5 (33.3)
Procedure, n (%)[b]						
Hysterectomy	7 (87.5)	26 (83.9)	16 (44.4)	19 (73.0)	22 (64.7)	5 (33.3)
Conservative	1 (12.5)	5 (16.1)	20 (55.6)	7 (27.0)	12 (35.2)	10 (66.7)

Annotation:
[a]The report was by the histologic study of the uterus (after hysterectomy or resection); [b]Procedure during manage the PAS (conservative was preserved the uterus by excision of the uterine corpus part where the placenta morbidly adherent)

Table 3 shows the number of bleeding during surgery. In group 1, blood loss reaches an average of 6025 cc and in group 2 the average bloodloss is 1719 cc. The difference of bloodloss between groups shows significantly value after integrated team was involved. Table 3 also shows that organ injuries duri ng PAS surgery. The bladder and ureter become the most damaged organ during this procedure. In group 1, the urologic injuries was 13 times while in group 2 only twice. It shows significantly difference after integrated team involved.

Table 3. Total Blood Loss and Organ Damage during Surgery

Year	N	Blood loss		Organ injury[b]		
		Mean + SD	*P-value*	Yes (%)	No (%)	*P-value*
2018 – 2020	75	6025 + 4224.86	.001[a]	13 (17.3)	62 (82.7)	.010[a]
2021 – 2023	75	1719 + 1987.76		2 (2.6)	73 (97.3)	

Annotation:
SD : Standard Deviation; CI 95% pvalue <0.05; *Mann-Whitney test;* [a]Significant value of the data, [b]Bladder and ureter were the most organ injury during the procedure

The group 1, show that more than half of patients' stays after surgery lasted longer than three days, with an average stay of 4.49 days. In comparison, from group 2, the average length of stay was three days, and less than 40% of patients stayed more than three days (Table 4). The difference between the two periods is statistically significant.

Table 4. Length of Stay after Surgery

Year	Length of Stay (days)				*Mean[a]*	*P-value*
	< 3	%	> 3	%		
2018 – 2020	35	46.7	40	53.3	4.49	.034[b]
2021 – 2023	46	61.3	29	38.7	3.00	

SD : Standard Deviation; CI 95% pvalue <0.05; *Mann-Whitney test;* [a]Average length of stay after surgery in days; [b]There is a significant value of the data.

DISCUSSION

The distinctive and proliferative characteristics of the placenta are closely associated with adverse maternal health outcomes, such as morbidity and mortality. Within the placenta accreta spectrum, the incidence of maternal mortality is concerning, currently standing at 7%. This rate can rise significantly to 30% when there is a lack of antenatal diagnosis.[9,10]. The Placenta Accreta Spectrum is linked to a markedly increased risk of severe hemorrhage, leading to pronounced coagulopathy. This condition is marked by multi-organ dysfunction, including cardiac arrest, respiratory insufficiency, cerebral hypoxia, sudden renal impairment, and systemic thrombotic events, ultimately resulting in maternal mortality.[11,12]. The probability of organ damage, particularly affecting the bladder, ureter, bowel, and vascular system, contributes to the increased incidence of maternal morbidity.[13]

The degree of complications and accompanying morbidity is intricately dependent on the antenatal capacity of the healthcare team to detect PAS disorder. Conversely, instances identified intraoperatively and managed by non-specialist medical personnel present an elevated likelihood of maternal morbidity and mortality[12,14]. The management of PAS at Dr. Moewardi Hospital is characterized by a significant level of interdisciplinary cooperation among its various medical departments based on the findings of several distinct research. From early 2021 we assembled collaboration from other medical fields into multidisciplinary teamwork according to the recommendation, including maternal-fetal medicine, gynecologic oncology, vascular and trauma surgery, urologic surgery, intensivists, neonatologists, interventional radiologists, anesthesiologists, and specialized nursing[8].

The first step in providing subspecialty care for patients with PAS by a multidisciplinary team involves accurate diagnosis and anticipating potential challenges[15]. Multiple investigations have demonstrated that instances suspected prenatally instead of postnatally exhibit decreased frequencies of hemorrhaging and other adverse maternal health outcomes[16]. The Second management alternatives comprise hysterectomy or conservative surgery, depending on the preoperative condition and the results obtained during the surgical procedure. Ensuring the well-being and survival of both the mother and child while considering the preservation of reproductive organs fosters the creation of an accomplished team characterized by optimal quality.[17]

The responsibility of maintaining fluid balance, administering vasopressors and blood products, and ensuring patient survival during surgery is

entrusted to the intensivist and anesthesiologist. Managing patients experiencing significant blood loss, unstable hemodynamics, and extended surgical procedures requires a crucial collaboration with anesthesiologists who possess extensive expertise in handling massive obstetric hemorrhage.[18] To minimize the risk of bladder or ureter injury and facilitate necessary reconstruction, the urology team will be present in the operating room during the cesarean section and hysterectomy. Additionally, the placement of urinary catheters reduces the risk of ureter injury and enables earlier detection of potential damage.[19]

Although the multidisciplinary approach implemented over the past three years has positively impacted PAS management, further strategies are needed to reduce bleeding complications and the incidence of PAS in the future.[2]

CONCLUSION

Multidisciplinary approaches by various medical department specialists are required to ensure the mother's safety. Integrated team will minimize blood loss and other complications. Periodic evaluation among the integrated team could have created better surgical procedure and improve the outcome in the future.

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Research Article

Anemia in Pregnancy and Its Maternal Perinatal Outcome

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Abstract

Objective: To investigate the relationship between anemia in pregnancy and maternal perinatal outcomes.

Methods: This was a retrospective cohort study. This research was held at Prof. Dr. R. D. Kandou General Hospital Manado. Data was taken from January 2021 to December 2022.

Results: There were 1953 deliveries which 1304 subjects (66.7%) with anemia 649 subjects with anemia (33.3%), 489 subjects with mild anemia, and 160 subjects with moderate-severe anemia. The median maternal age was 28 years for mild anemia. The majority of mothers have a high school education. A total of 326 study subjects were multigravidas with mild anemia. The results of severe preeclampsia with mild anemia were 30 subjects. Prolonged labor tends to be higher in the mild anemia group. The highest distribution was observed in the mild anemia group, with 12 cases of maternal mortality, 88 cases of premature birth, 78 cases of low birth weight (LBW), 75 cases of disorders leading to decreased scores, and 24 cases of fetal mortality. In research subjects, IUGR tends to be more common in groups with moderate-severe anemia with 14 subjects (8.8%). Hemoglobin levels showed a median of 11.6 g/dL with a distribution midway between 10.5 and 12.6 g/dL. The mean MCV value is 76.1 fL (SD 8 fL). The mean MCH value was 24.8 + 3.6 pg. The MCHC value is 32.5%. Conclusions: There are no significant relation in pregnant women with anemia with preeclampsia, prolonged labor, maternal mortality rate and IUGR, but there are significant relation between anemia in pregnancy with increase rate of caesarean section, premature delivery, low birth weight, low APGAR score and fetal death.

Keywords: anemia in pregnancy, maternal outcome, neonatal outcome.

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INTRODUCTION

Anemia is a global health issue that also affects pregnant women. The prevalence of anemia varies according to socioeconomic status and lifestyle factors. It is primarily caused by iron deficiency, followed by other micronutrient deficiencies, infections, and hereditary hemoglobinopathies.[1] Forty percent of pregnant women worldwide are anemic, with 56% of women in low- to moderate-income countries affected.[2,3] Indonesia has shown an upward trend in the prevalence of anemia from 2015 to 2019. Among ASEAN countries, Indonesia ranked fourth highest in the prevalence of anemia during pregnancy in 2019, with a rate of 44.2%, while Cambodia had the highest rate at 47.8%.[4] Anemia in pregnancy in North Sulawesi in 2018 was 455 cases and this is increased from 2017 which are 339 cases, while in Manado itself there was 11% pregnant women with anemia[5].

Anemia in pregnancy is related to adverse outcomes and increases the risk of maternal and perinatal mortality rates. Various research shows that anemia in pregnancy contributes to 23% indirect cause of maternal mortality rate in developing countries.[5-7] Maternal outcomes of anemia in pregnancy are preeclampsia, hemorrhagic postpartum, and maternal mortality. Research showed that severe anemia in pregnancy has 3 times the risk of preeclampsia.[8-11] Perinatal outcomes that can happen in anemia in pregnancy are premature delivery, low birth weight, intrauterine fetal death (IUFD), low APGAR score, and intrauterine growth restriction

(IUGR).[9,12-15] Similar results show that anemia in pregnancy has lower birth weight outcomes.15 This research aimed to analyze the relation between anemia in pregnancy and maternal and perinatal outcomes, and further quantify the risk.

METHODS

This was a retrospective cohort study with primary data from blood work and secondary data from pregnant women who delivered at the research site. This research was held at Prof. Dr. R. D. Kandou General Hospital Manado, and the data taken was from January 2021 to December 2022 with the number of ethical clearance No. 239/EC/KEPK-KANDOU/XI/2022. The inclusion criteria for this research were women with a gestational age of > 20 weeks and blood works of hemoglobin level, MCV, MCH, and MCHC. Women with chronic diseases like tuberculosis and malignancy were excluded. Data taken was then analyzed using Fisher's test and the Kruskal-Wallis test according to the variable. At the same time, the correlation of anemia in pregnancy with the outcomes was analyzed with a logistic regression model.

RESULTS

There were 1953 deliveries with 1304 subjects (66.7%) with non anemia and 649 subjects with anemia (33.3%), with 489 subjects with mild anemia and 160 subjects with moderate-severe anemia Table 1 showed the characteristics of research subjects.

Table 1. Characteristic of Research Subjects

Characteristics	Mild Anemia		Moderate-Severe Anemia	
	n (%)	Median (Q1;Q2)	n (%)	Median (Q1;Q2)
Maternal age		28 (23-33)		26 (22-32)
< 20	63 (12.8)		21 (13.1)	
20-35	338 (69.2)		115 (71.9)	
> 35	88 (18)		24 (15)	
Maternal educational level				
Junior high/lower	105 (21.5)		46 (28.8)	
Senior high	268 (54.8)		85 (53.1)	
Diplome/Bachelor	116 (23.7)		29 (18.1	
Parity				
Primigravida	163 (33.3)		51 (31.9)	
Multigravida	326 (66.7)		109 (68.1)	
Total ANC		5 (2-7)		3 (1-5)
Never	76 (15.5)		32 (20)	
1-3	94 (9.2)		50 (31.3)	
> 4	319 (65.3)		78 (48.7)	
ANC provider				
General practitioner/Clinic	16 (3.3)		4 (2.5)	
Primary Health Care/Midwife	125 (25.6)		48 (30)	
Obgyin/Hospital	272 (55.6)		76 (47.5)	
Never	76 (15.5)		32 (20)	

NOTE: Characteristic and distribution of research subjects

From all the deliveries taken within the period, we obtained 649 subjects with anemia, where 489 and 160 subjects had mild anemia and moderate-severe anemia respectively. There were 338 (69,2%) research subjects who delivered at 20 – 35 years old in the mild anemia group and 115 (71.9%) in the moderate-severe anemia group. Most of the research subjects (348/649 research subjects, 53.6%) did antenatal in hospital with an OBGYN specialist, and more than 60% of subjects went for antenatal care > 4x visits. Table 2. describes the distribution of maternal and perinatal outcomes for research subjects with mild and moderate-severe anemia. Maternal and perinatal outcomes are categorized as preeclampsia, prolonged labor, cesarean section, maternal mortality, premature delivery, low birth weight, low APGAR score, IUGR, and IUFD.

Table 2. Maternal and Perinatal Outcome

Characteristics	Mild Anemia	Moderate-Severe Anemia
	n (%)	n (%)
Preeclampsia/Eclampsia		
Not preeclampsia	434 (88.8)	143 (89.4)
Preeclampsia	6 (1.2)	1 (0.6)
Severe Preeclampsia	30 (6.1)	13 (8.1)
I mpending eclampsia – eclampsia	19 (3.9)	3 (1.9
Prolonged labor	20 (4)	9 (5.6)
Delivery method		
Vaginal delivery	166 (33.9)	50 (31.3)
Cesarean section	323 (66.1)	108 (67.5)
Maternal Mortality	12 (2.5)	0
Premature Delivery	88 (18)	38 (23.7)
Low Birth Weight	78 (16)	41 (25.6)
APGAR 5'	75 (15.3)	47 (29.4)
IUGR	12 (2.5)	14 (8.8)
IUFD	24 (4.9)	22 (13.8)

Notes: SD standard deviation, Q1 quartile I, Q3 quartile III, Low Birth Weight (< 2500 g), IUGR *intrauterine growth restriction* according to Lubchenco

Table 2 shows that prolonged labor tends to occur in the mild anemia group. In contrast, IUGR tend to occur more in the moderate-severe group.

Table 3. Classification and Degree of Anemia

Characteristics	*n* (%)	Mean ± SD	Med (Q1; Q3)	
Hemoglobin (g/dL)			11.6	(10.5 ; 12.6)
MCV (fL)		76.1 + 8		
Normocytic	169 (9)			
Microcytic	303 (16)			
MCH (pg)		24.8 + 3.6		
Normochromic	175 (9)			
Hypochromic	297 (15)			
MCHC (%)				
Anemia status			32.5	(31 ; 33,7)
Non-Anemia (Hb > 11 g/dL)	1304 (67)			
Mild (Hb 9 – 10.9 g/dL)	489 (25)			
Moderate (Hb 7 – 8.9 g/dL)	125 (6.3)			
Severe (Hb < 7 g/dL)	35 (1.7)			
Classification of Anemia				
Normocytic Normochromic	139 (7)			
Normocytic Hypochromic	30 (1.5)			
Microcytic Normochromic	36 (1.8)			
Microcytic Hypochromic	267 (13.7)			

Notes: SD standard deviation, Q1 quartile I, Q3 quartile III, MCV mean corpuscular volume, MCH mean corpuscular hemoglobin, MCHC mean corpuscular hemoglobin concentration

Hemoglobin concentration showed a median of 11.6 g/dL with a range of 10.5 and 12.6 g/dL. The average MCV value was 76.1 fL (SD 8 fL). MCV value showed the result was below normal value, indicating that the erythrocytes tend to be smaller in size (mycrocytic). The MCH value was 27-35pg. In this research mean MCH values were 24.8 + 3.6 pg with MCHC value 32.5%. Table 4 describes the relation between anemia in pregnancy and maternal and perinatal outcomes with univariate and multivariate regression models to analyze the odds ratio.

Table 4. Maternal and Perinatal Outcome in Relation of Anemia in Pregnancy with Non-Anemia on Univariate and Multivariate Regression Model

Outcome	Univariate		Multivariate	
	***OR* (95% CI)**	***P-value***	***OR* (95% CI)**	***P-value***
Preeclampsia/ Eclampsia	0.52 (0.40 ; 0.68)	< 0,001	0.53 (0.40 ; 0.69)	< 0.001
Prolonged Labor	0.72 (0.43 ; 1.20)	0.208	0.68 (0.41 ; 1.14)	0.146
Caesarean Section	1.04 (0.85 ; 1.27)	0.708	4.33 (2.70 ; 6.96)	< 0.001
Maternal Mortality	1.06 (0.45 ; 251)	0.899	0.00 (0.00 ; 0.0)	0.985
Prematurity	1.03 (0.78 ; 1.34)	0.848	1.79 (1.20 ; 2.67)	0.004
Low Birth Weight	1.01 (0.80 ; 1.27)	0.953	1.60 (1.12 ; 2.27)	0.009
APGAR 5' (β)*	-0.28 (-0.47 ; -0.09)	0.003	-0.65 (-0.96 ; -0.34)	< 0.001
IUGR	1.15 (0.84 ; 1.56)	0.384	1.10 (0.80 ; 1.50)	0.557
Fetal Death	1.59 (1.04 ; 2.43)	0.032	1.62 (1.06 ; 2.48)	0.026

NOTES: CI *confidence interval,* OR odds rasio, Low Birth Weight (< 2500 g), IUGR *(intrauterine growth restriction)* according to Lubchenco. * Linear coefficient regression to evaluate APGAR score

Table 4 showed there is no significant relation between anemia in pregnancy and preeclampsia/ eclampsia (p<0.001) and prolonged labor (p<0.146). Anemia in pregnancy related with increase rate of caesarean section by almost 4.33 times in compared with non anemic patient (OR 4.33, p<0.001). there is significant relation between anemia in pregnancy and the incidence of premature delivery (p<0.004). low birth weight (p<0.009), low APGAR score (p<0.001) and fetal death (p<0.026). While there is no significant relation between IUGR and anemia in pregnancy (p<0.557).

DISCUSSION

This research showed no relation between anemia in pregnancy and preeclampsia (Univariate OR 0.52 %, 95% CI 0.4 – 0.68, P < 0.001 vs multivariate OR 0.53 %, 95% CI 0.4 – 0.69, P < 0.001). The mechanism of preeclampsia in anemia in pregnancy is caused by micronutrient deficiency. In this mechanism, norepinephrine induces the synthesis of corticotropin-releasing hormone (CRH) which is produced by the placenta. CRH stimulates inflammatory cytokines, glucocorticoid, and oxidative stress. Oxidative stress stimulates angiotensin receptor 1-autoantibodies (AT1-AAs) which induce sFlt-1 and sEng which bind to vascular endothelial growth factor (VEGF) and placental growth factor (PIGF). This condition affects systemic vascular resistance.

A previous study described the relationship between anemia in pregnancy with preeclampsia. Severe anemia has the tendency of preeclampsia up to 3 times higher. Another research was done at Airlangga University Hospital Surabaya where there was no significant relation between anemia in pregnancy and preeclampsia. This relation might be due to an increase in plasma volume with a reduction of hemoglobin level which causes hemodilution while MCV, MCH, and MCHC tend to increase. [16,17]

In this research, there is no relation between anemia in pregnancy with prolonged labor (Univariate OR 0.72%, 95% CI 0.43 – 1.20, P 0.208 vs Multivariate OR 0.68%, 95% CI 0.41 – 1.14, P 0.146). This result differs from several studies that support anemia in pregnancy related to the progressivity of delivery during stage one labor and weakening of contraction at stage two. Prolonged stage one might happen because of low hemoglobin levels causing the reduction of the circulating oxygen level to the brain. Hence the oxygen level to the uterus is also reduced causing weakening of uterine contraction, causing cervical ripening to become prolonged.[18,19] This difference might be because of most of our research subjects have mild anemia. Several studies showed that moderate-severe anemia may cause prolonged labor. Mothers with moderate-severe anemia tend to prolong the labor compared with mild anemia (OR 4.681).[20]

This research found that there is no significant relation between anemia in pregnancy and maternal mortality (Univariate OR 1.06%, 95% CI 0.45 – 2.51, P 0.899 vs multivariate OR 0.00, 95% CI 0.00 – ∞, P 0.985). There is a discrepancy between the univariate and multivariate tests. During this study period, 17 out of a total of 23 subjects (73.91%) were affected. At least the total sample and cause of date is COVID-19 which might affect the sample. Severe anemia reduces the availability of oxygen in tissue, reduces iron for DNA synthesis, and changes enzyme function

all of which contribute to the association of anemia in pregnancy and maternal mortality. Severe anemia gives a 2.36 times higher chance mother with severe anemia death.

There is significant relation between anemia in pregnancy and premature delivery. In this study the chance of premature delivery increase as high as 1.79 times compared to non anemic patient (Univariate OR 1.03%, 95% CI 0.78 – 1.34, P 0.848 vs multivariate OR 1.79, 95% CI 1.20 – 2.67, P 0.004). Anemia cause tissue hypoxia and directly increase corticotropin hormone (CRH) release, which induce delivery. CRH also can inhibit fetal growth.[21-23] This result is in accordance with several previous research. There is 4 times chance of premature delivery with anemia in pregnancy.[21] Sixty one percent anemic mother had adverse perinatal outcome which one of them is preterm delivery (22.2%).[22]

There is significant relation between anemia in pregnancy and low birth weight. Anemia in pregnancy increase the incidence of low birth weight about 1.6 times then non anemic mother (Univariate OR 1.01%, 95% CI 0.80 – 1.27, P 0.953 vs multivariate OR 1.6, 95% CI 1.12 – 2.27, P 0.009). This research is in accordance with several research where anemia in pregnancy causing low birth weight (birth weight <2500 g). The risk of low birth weight in mother with anemia increase 1.9 times compared to non anemic mother.[21] Anemia in pregnancy causing changes in hemoglobin concentration level which related to birth weight.[23]

Anemia in pregnancy tend to lower APGAR score (Univariate OR -0.28%, 95% CI -0.47 – (-0.09), P 0.003 vs multivariate OR -0.65, 95% CI -0.96 – (-0.34), P < 0.001). The risk of APGAR score within 1 minute is < 5 and within 5 minutes is < 7 and tend to be lowered in anemic mother.[21] Fourty out of 405 pregnant women had APGAR score < 7 in the first 1 minute and 5 minutes.[23]

In this research there is no significant relation between anemia in pregnancy and IUGR (Univariate OR 1.15%, 95% CI 0.84 – 1.56, P 0.384 vs multivariate OR 1.1, 95% CI 0.80– 1.50, P 0.557). Even though there was a tendency for the probability of IUGR to increase in more severe anemia. To explain the mechanism of anemia in pregnancy for causing adverse perinatal outcome, several aspect can be seen like uteroplacental circulation. In anemia in pregnancy the amount of oxygenated blood towards uteroplacental circulation is low and lowered nutrient distribution, thus causing fetal growth restriction.

There was a significant relation between fetal mortality and anemia in pregnancy. Anemia in pregnancy increases fetal mortality rate as high as 1.62 times compared to nonanemic mother (Univariate OR 1.59%, 95% CI 1.04 – 2.43, P 0.032 vs multivariate OR 1.62, 95% CI 1.06 – 2.48, P 0.026). Severe anemia further worsens the fetal mortality. Studies showed that 61.9% of anemia in pregnancy causes adverse perinatal outcomes like IUFD or stillbirth as high as 1.5%.24 While research from Rahman et al showed perinatal mortality (OR, 2.90; 1.97-3,78, p < 0,05) in anemic mothers during pregnancy[23] Disease or inadequate nutrition during pregnancy further disrupts fetal growth. Thus causing low birth weight, premature delivery, and stillbirth. These factors are the primary contributors to neonatal mortality.[24]

CONCLUSION

There is no significant relation between mothers with anemia in pregnancy with preeclampsia, prolonged labor, IUGR, and maternal mortality. There was a significant relation between anemia in pregnancy with an increased rate of cesarean section, premature delivery, low birth weight, low APGAR score, and fetal mortality.

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Research Article

The Impact of Gestational Weight Gain on Preeclampsia during COVID-19 Pandemic

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Abstract

Objective: To determine the impact of weight gain in pregnant women on the incidence of preeclampsia during the COVID-19 pandemic at the West Lombok District Health Center

Methods: This research is an analytical observational study using a case control study. The design began by identifying patients with impacts (preeclampsia and/or eclampsia) and groups without impacts (not experiencing preeclampsia and/ or eclampsia), then exploring risk factors in 3 Community Health Centers located in West Lombok Regency, NTB Province, Indonesia, especially Narmada Health Center, Kediri and Gunung Sari. Analysis was carried out using the SPSS application.

Results: A total of 120 samples were collected, comprising 60 case samples and 60 control samples. During the 2020-2021 COVID-19 pandemic, individuals with weight gain that did not meet the recommended guidelines exhibited a higher incidence of preeclampsia, with 56 individuals (93.3%) affected, compared to 32 individuals (53.3%) in the control group without preeclampsia. The calculated odds ratio (OR) was 12.25, with a 95% confidence interval of 3.941 to 38.078.

Conclusion: There is an increased risk of preeclampsia in pregnant women during the COVID-19 pandemic, which is associated with gestational weight gain. Early screening for preeclampsia is essential if future pandemic outbreaks alter daily human activity patterns.

Keywords: COVID-19, eclampsia, gestational weight gain, preeclampsia.

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INTRODUCTION

The maternal mortality rate (MMR) reflects the health and mortality status of mothers during pregnancy and childbirth. MMR is influenced by both direct and indirect causes. Direct causes include complications arising from pregnancy or childbirth. Indirect causes encompass pre-existing diseases or conditions acquired during pregnancy that impact the course of pregnancy and childbirth.[1]

In 2017, fifteen countries—South Sudan, Somalia, Central African Republic, Yemen, Syria, Sudan, Democratic Republic of the Congo, Chad, Afghanistan, Iraq, Haiti, Guinea, Zimbabwe, Nigeria, and Ethiopia—were classified as being on "very high alert" or "high alert" due to elevated maternal mortality rates (MMR). The MMR for these countries ranged from 31 to 1150 per 100,000 live births.[2] Young women under the age of 15 face the highest risk of maternal death. Those aged 10 to 19 are more likely to experience complications during pregnancy and childbirth compared to women aged 20 to 24.[2,3]

Since February 2020, the COVID-19 pandemic has impacted every country globally. Pregnant women are more susceptible to severe illness during the COVID-19 pandemic compared to non-pregnant women. Changes in lifestyle and activity patterns have been necessary to adapt to pandemic conditions, particularly regarding food consumption, dietary habits, and the shift to work from home (WFH) and learn from home (LFH) activities. These adjustments have led to an increased risk of weight gain, obesity, and elevated Body Mass Index (BMI) due to an

imbalance between food intake and physical activity.[4] Additionally, COVID-19 transmission can exacerbate pre-existing conditions and negatively affect pregnancy outcomes. Adverse pregnancy outcomes, such as preeclampsia and eclampsia, are among the risks heightened by the pandemic.[5]

Preeclampsia, which can progress to eclampsia, is one of the three primary causes of morbidity and mortality among pregnant women globally.[6] Maternal risk factors such as hydatidiform moles, nulliparity, multiple pregnancies, chronic hypertension, diabetes mellitus, and kidney disease increase the incidence of preeclampsia. The risk of developing severe preeclampsia or eclampsia is three times higher in mothers over 35 compared to those under 35. Additionally, preterm pregnancies are 2.4 times more likely to experience severe preeclampsia or eclampsia deterioration compared to term pregnancies, despite the higher risk of severe preeclampsia-eclampsia in term pregnancies.[7]

Health services focused on managing COVID-19 in affected countries have led to a decline in various medical services, including obstetrics and gynecology clinics. Therefore, pregnant women require increased attention to their pregnancy status. Nutritional status during pregnancy is a significant concern. Insufficient maternal weight gain can result in children being born to malnourished mothers, who are then at risk of malnutrition and infection, potentially leading to malnourished adults. Conversely, excessive weight gain during pregnancy can cause complications and poor maternal outcomes.[8]

However, there is limited research on preeclampsia during the COVID-19 pandemic or other similar health crises. This study aims to investigate the impact of gestational weight gain, influenced by changes in daily activity patterns during the COVID-19 pandemic, on preeclampsia. The research will be conducted at three Community Health Centers in West Lombok Regency, Indonesia.

METHODS

This case-control study utilized data from the Narmada, Kediri, and Gunung Sari Health Centers, three community health centers in West Lombok Regency, West Nusa Tenggara Province, Indonesia. Data collection was obtained from medical records from August to September 2022. The study aimed to identify patients affected by preeclampsia and/or eclampsia (case group) and those unaffected (control group). The study population comprised pregnant women aged 20 to 35 years registered at the West Lombok District Health Center during the 2020–2021 period, in their second or third trimester. All diagnosed cases of preeclampsia and eclampsia during this period were included. The sample size of 58 for each group (case and control) was determined using the paired case-control formula in the Epi Info software developed by the Centers for Disease Control and Prevention (CDC). A total of 125 samples were collected: 60 from the case group, 60 from the control group, and 5 were excluded due to incomplete medical records.

Pregnant women diagnosed with eclampsia or preeclampsia comprised the case group in this study, while those without these diagnoses constituted the control group. Preeclampsia can be further classified into early-onset and late-onset groups based on gestational age (GA), typically categorized using cutoff points at GA 34 weeks or GA 37 weeks. This classification allows for subgroups of early-onset (GA < 34 weeks) and late-onset (GA ≥ 34 weeks) preeclampsia.

Independent variable was maternal body mass index (BMI) increase during pregnancy, tracked through recorded weight gain data from medical records. The dependent variable was the incidence of preeclampsia and/or eclampsia. BMI classifications used in this research were based on World Health Organization (WHO) criteria for Asians and body mass index criteria from the Republic of Indonesia's Ministry of Health. These classifications included underweight (<18.5 kg/m^2), normal weight (18.5-22.9 kg/m^2), overweight (23-24.9 kg/m^2), grade 1 obesity (25.0-29.9 kg/m^2), and grade II obesity (≥30.0 kg/m^2).

The Institute of Medicine's recommendations, which are shown in the following table (Table 1), served as the study's reference for increasing body weight. The Statistical Product and Service Solutions (SPSS) program is then used to process the acquired data, and the chi-square statistical test is used to analyze the data both univariately and bivariately.

RESULTS

Table 1. Category of Weight Gain during Pregnancy Based on BMI

Categories	Gestational Weight Gain based on BMI (kg/m²)			
	BMI			
	<18.5	18.5-24.9	25.0-29.9	≥30.0
Deficient	< 12.7	< 11.3	< 6.8	< 5.0
Appropriate	12.7-18.1	11.3-15.8	6.8–11.3	5.0–9.1
Exceed	> 18.1	> 15.8	> 11.3	> 9.1

BMI: Body Mass Index (kg/m²), kg: kilogram

Table 2. Impact of Sample Characteristics on Preeclampsia and Eclampsia

Sample Characteristics	Preeclampsia/ Eclampsia (Cases)		Normal (Control)		Normal (Control)	*P-Value*
	n	%	n	%		
Age (Years)	Mean (SD) = 2.25 (0.73622)					
20-25	10	16.7	11	18.3		
26-30	17	28.3	31	51.7		
31-35	33	55	18	30	-	0.105
Amount	60	100	60	100		
Gravida Status	Mean (SD) = 1.8083 (0.91022)					
Multigravida	57	95	59	98.3		
Grandemultigravida	3	5	1	1.7	-	0.619
Amount	60	100	60	100		
Jobs	Mean (SD) = 1.55 (1.36493)					
Unemployment	52	86.7	48	80		
Private	0	0	3	5		
Self-Employed	3	5	1	1.7		
Civil Servants	1	1.7	1	1.7	-	0.413
Teachers	2	3.3	4	6.6		
Traders	2	3.3	3	5		
Amount	60	100	60	100		
BMI Before Pregnancy	Mean (SD) = 3.225 (1.18437)					
Underweight	2	3.4	5	8.3		
Normal	13	21.6	21	35		
Overweight	7	11.7	15	25		
Obesity 1	25	41.7	14	23.4	2.3	0.013
Obesity 2	13	21.6	5	8,3		
Amount	60	100	60	100		
Trimester	Mean (SD) = 1.9333 (0.25049)					
TM-2	8	13.3	0	0		
TM-3	52	86.7	60	100	-	0.003
Amount	60	100	60	100		

BMI: Body Mass Index, SD : Standard deviation, CI : Confidence Interval, OR : Odds Ratio

Table 3. Impacts of Weight gain on the incidence of preeclampsia

Gestational Weight Gain Mean (SD) 1.7333 (0.44407)	Preeclampsia				OR 95% CI	*P-Value*
	Yes		No			
	n	%	n	%		
Appropriate	4	6.7	28	46.7	12.250	0.000002
Inappropriate	56	93.3	32	53.3	(3.941-38.078)	
Total	60	100	60	100		

DISCUSSION

Impact of Sample Characteristics on Preeclampsia and Eclampsia

Preeclampsia was found to be highly prevalent among women aged 31 to 35 during the COVID-19 pandemic. The analysis conducted in the catchment areas of Narmada, Kediri, and Gunung Sari Health Centers indicated no significant correlation between age and the incidence of preeclampsia and eclampsia (P-value = 0.105). These findings align with a study conducted at RSI Ibnu Sina Simpang Ampek, West Pasaman Province, West Sumatra, by Maya Fernanda Dielsa, which similarly found no association between maternal age within the non-risk range (20-35 years) and preeclampsia.[9] The optimal age range for pregnancy and childbirth is typically considered to be between 20 and 35 years. During this period, maternal reproductive organs are fully developed and functional. However, pregnancies at younger than twenty or older than thirty-five years carry higher risks, impacting fertility and maternal outcomes.[9,10]

During the COVID-19 pandemic, multigravida women showed a higher incidence of preeclampsia. However, the study's analysis found no significant correlation between gravida status and the incidence of preeclampsia and eclampsia (P-value = 0.619). These findings align with research conducted at RSUP Dr. M. Djamil Padang from 2012 to 2013, which indicated 1.3 times fewer cases of preeclampsia among multigravida women compared to primigravida women. Mothers with multiple pregnancies exhibit an immune response involving HLA-G (human leukocyte antigen G), which generates antibodies that inhibit certain substances targeting placental antigens formed during previous pregnancies. This mechanism potentially enhances trophoblast implantation into the mother's decidual tissue compared to first pregnancies.[10]

Pregnant women who were not employed showed a higher incidence of preeclampsia, based on the number of cases observed within each occupational group. However, in the catchment areas of Narmada, Kediri, and Gunung Sari Health Centers, there was no significant correlation between the incidence of preeclampsia and eclampsia and employment status, as indicated by research analysis results (P-value = 0.413). This lack of association holds true regardless of whether the COVID-19 pandemic was occurring.[11]

This finding suggests that the incidence of preeclampsia is not directly linked to employment status but rather to stress levels. Pregnant women who are not employed may be at higher risk of experiencing preeclampsia due to stress associated with various household issues such as economic difficulties, family problems, and anxiety related to pregnancy and childbirth.[12] Furthermore, individuals who have lost their jobs during a pandemic may also experience weight gain due to stress arising from financial insecurity, which affects their ability to afford daily nutritional needs.[13]

During the COVID-19 pandemic, preeclampsia was notably prevalent among women classified with grade 1 obesity, as observed in the number of pregnant women affected compared to those without preeclampsia, based on their pre-pregnancy BMI status. Analysis of the study's data revealed a significant correlation between the incidence of preeclampsia and eclampsia and pre-pregnancy BMI status (P-value = 0.013, OR 2.3, CI = 1.056-4.985). These findings are consistent with another study conducted at the Sepatan Health Center in Tangerang Regency, which also identified a link between preeclampsia incidence and maternal BMI prior to pregnancy (P-value = 0.007, OR 12.250, CI = 2.185-68.692).[14]

The study's findings support the hypothesis that elevated BMI levels contribute to insulin resistance, characterized by hyperinsulinemia, hyperlipidemia, hypertension, and endothelial dysfunction. Higher BMI correlates with increased lipid peroxide levels and reduced pregnancy-related antioxidants, potentially damaging endothelial cell membranes.[15] Researchers suggest that the COVID-19 pandemic has led to a shift in social activity patterns towards sedentary behaviors, which may contribute to increased body weight and BMI.

From 60 patients in the case group, 52 patients experienced preeclampsia in the third trimester compared to patients in the same group who experienced preeclampsia in the second trimester (Table 2). The analysis of this study's data also revealed a significant correlation between the incidence of preeclampsia and eclampsia and the trimesters of pregnancy (P-Value = 0.003). The findings of this investigation are consistent with those of other studies. Preeclampsia incidence during the COVID-19 pandemic was influenced by gestational age in the years leading up to and including the pandemic (2019–2020) (P-Value =

0.002; OR=3.59).[16]

The theory that higher gestational age increases the risk of preeclampsia and eclampsia is supported by the prevalence of these conditions, which are more common in the third trimester of pregnancy. In a normal physiological pregnancy, spiral arteries in the decidua undergo cell turnover facilitated by endovascular trophoblasts. This turnover process ensures that the arteries remain open, providing continuous blood flow, adequate nutrition, and balanced oxygen levels. Ideally, this cell turnover should be completed by the 16th week of pregnancy, coinciding with the completion of placental formation. In cases of preeclampsia or eclampsia, inadequate invasion of trophoblasts occurs, particularly in the uterine arteries, leading to restricted blood flow. This uteroplacental ischemia results in insufficient delivery of nutrients and oxygen to the placenta, exacerbating the condition.[17]

The Impact of Weight Gain on the Incidence of Preeclampsia and Eclampsia in the COVID-19 Pandemic

A significant correlation (P-value of 0.000002, <0.05) was found between weight gain and the incidence of preeclampsia during the COVID-19 pandemic, based on research analysis results. The study also determined an Odds Ratio of 12.25 (95% Confidence Interval, 3.941-38.078), indicating that pregnant patients who did not meet recommended weight gain guidelines during the COVID-19 pandemic were 12.25 times more likely to experience preeclampsia compared to those who adhered to the recommended weight gain guidelines.

Late-onset preeclampsia, occurring at ≥34 weeks of gestation (3rd trimester), predominantly affects pregnant women who have had multiple pregnancies. In contrast, early-onset preeclampsia is more common among women experiencing their first pregnancy. This observation suggests that prolonged exposure to sperm may confer a protective effect against preeclampsia, in line with the immune maladaptation theory. According to this theory, women who have been pregnant multiple times are less likely to develop preeclampsia compared to those in their first pregnancy. However, while multiparas generally have a lower risk, it does not eliminate the possibility of preeclampsia.[18] Late-onset preeclampsia is primarily linked to factors such as increased maternal body mass index (BMI), gestational weight gain, and associated clinical features like metabolic syndrome.[19]

The COVID-19 pandemic, impacting the global population since 2020, has precipitated significant alterations in lifestyle habits. These changes have largely resulted from lockdown measures, widespread social restrictions, and directives to remain at home. The consequence of prolonged home confinement includes unintended outcomes such as weight gain, reduced physical activity, and increased social isolation.[20]

Two significant factors are associated with changes in lifestyle habits during the COVID-19 pandemic. First, staying at home necessitates remote learning, telecommuting, or extended computer use without outdoor activities. Second, food storage at home becomes crucial due to restrictions on outdoor food purchases. Moreover, disruptions to work schedules during quarantine can lead to boredom, which may contribute to increased calorie consumption. Elevated stress levels during the pandemic may also lead to overeating, particularly of carbohydrate-rich foods, thereby increasing the risk of obesity.[21]

Excessive weight gain in mothers leads to an increase in adipocyte accumulation. Adipose tissue secretes leptin and adiponectin; leptin exhibits pro-inflammatory properties, while adiponectin exerts anti-inflammatory effects by reducing the expression and release of pro-inflammatory cytokines.[22] Consequently, elevated weight gain and BMI levels contribute to insulin resistance, characterized by hyperinsulinemia, hyperlipidemia, hypertension, and endothelial dysfunction.[15] Individuals with high BMI, metabolic syndrome, and type 2 diabetes mellitus typically exhibit reduced plasma adiponectin levels and increased levels of pro-inflammatory cytokines such as TNF-α and interleukin-6 (IL-6). This inflammatory state contributes to endothelial dysfunction and insulin resistance.[22]

Obesity or excess body weight not only elevates blood cholesterol levels but also contributes to insulin resistance. This insulin resistance can raise blood pressure during pregnancy by activating the sympathetic nervous system, promoting renal sodium retention, and increasing cation transport. It is also associated with endothelial dysfunction, which can lead to multi-organ abnormalities. The syndrome of insulin resistance plays a significant role in the pathogenesis of preeclampsia. This is consistent with previous studies that have linked elevated levels of all lipid profile parameters with an increased incidence of preeclampsia.[23]

Endothelial dysfunction can induce microvascular damage to target organs, intravascular inflammation characterized by a cytokine storm, and activation of thrombin. These processes collectively contribute to the multisystemic nature of the syndrome, involving manifestations such as seizures and central nervous system dysfunction alongside renal complications. Consequently, infections that target the endothelium can lead to syndromes like preeclampsia and eclampsia.[24]

Severe hypertension, headache, ankle clonus, epigastric or right upper quadrant pain, and visual disturbances are among the common early signs of eclampsia. Research investigating the relationship between these symptoms and significant risk factors for eclampsia development in patients already diagnosed with severe preeclampsia is limited. It's important to note that the severity of hypertension alone does not reliably indicate the likelihood of developing eclampsia..[25]

LIMITATIONS

This study utilizes secondary data, which comes with inherent limitations such as variables that were not directly measured by researchers. The data obtained from patients' medical records also includes limitations that are beyond the researchers' control. Additionally, certain variables have not been studied, including the presence of edema in preeclampsia, stress factors related to the COVID-19 pandemic, and exposure to SARS-CoV-2 among pregnant women. These factors could potentially influence the incidence of preeclampsia and eclampsia during the COVID-19 pandemic.

CONCLUSIONS

This study proposes that the COVID-19 pandemic increases the likelihood of preeclampsia in pregnant women due to gestational weight gain. Early screening for preeclampsia is crucial in the event of future pandemic outbreaks that alter daily human activity patterns. Community Health Centers can play a pivotal role as the primary providers of preeclampsia screening for pregnant women.

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Research Article

Peripheral Serum AMH and FSH Levels for Determining Ovarian Reserve in Experimental Mouse Model

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ABSTRACT

Objective: To determine peripheral serum levels of AMH and FSH in experimental animals for predicting ovarian reserve.

Methods: This is an experimental study was conducted from March 2022 to May 2023 at the Indonesia Medical Education and Research Institute (IMERI) and Integrated Laboratory and Histology Laboratory of the Faculty of Medicine, Universitas Indonesia (FKUI) and involving 20 female Sprague-Dawley rats aged 8–10 weeks with normal estrus cycles and 5 female rats aged 28–30 weeks. The experiment is divided into 5 groups, the young age control group, the old age control group, the 1x cisplatin group, the 2x cisplatin group, and the 3x cisplatin group. Cisplatin is one of the chemotherapeutic agents that has moderate toxicity employed to reduce ovarian reserve in a rat model. Intraperitoneal injection of cisplatin at 2 mg/kg/day twice a week for five weeks significantly decreases ovarian reserve, as evidenced by a notable reduction in Anti-Mullerian Hormone (AMH) levels. After the treatment, tissue collection, histological staining, peripheral and central blood collection through the retro-orbital bleeding (ROB) and heart were performed.

Conclusion: In the follicle count, the group treated with cisplatin 2x exhibited a significantly lower number of live follicles compared to the cisplatin 1x and 3x groups. The average concentrations of serum AMH and FSH in the ROB and heart were higher in the 2x cisplatin group compared to the other groups. The more cisplatin added the more ovarian reserve reduced and it corresponds to the old age control group. The increase in the follicles count and decrease in serum level in the cisplatin 3x group was due to the burn out phenomenon. Blood collection through the ROB is considered a less invasive alternative technique in the treatment group, requiring serial observation.

Keywords: AMH, animal model, follicle pool, ovarian aging, ROB.

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INTRODUCTION

Menopause is the end of a woman's reproductive phase. However, a decline in fertility can be seen in the last 20 years before menopause, and 10 years before menopause, the ability to become pregnant becomes significantly low. Ovarian aging stands out as a primary factor in the decline of female fertility associated with age. It involves a progressive decrease in the quantity and quality of oocytes, while the physiology of ovarian aging means a specific decline in the functional ovarian reserve over a defined period. The female ovarian reserve diminishes progressively with advancing chronological age.[1] The passage of time since birth is what determines chronological age. In contrast, physiological rather than chronological factors determine biological age. Chronological and biological aging are different from one another, with genetic and environmental factors influencing biological age. Reproductive function is more significantly influenced by biological age than chronological age. Knowing the biological age of a woman's ovaries and the subsequent pattern of decline is very important for assisted reproductive technology (ART), as it can determine the subsequent course of management. Ovarian reserve serves as a reliable marker for determining biological age.[2] The true ovarian reserve can be determined through the histological counting of ovarian follicles. However, this method is invasive, necessitating less invasive measures, one of which is through serum levels of AMH (Anti-Müllerian Hormone) and FSH (Follicle-Stimulating Hormone).[3]

Anti-Mullerian Hormone (AMH) and antral follicle count (AFC) are widely used as ovarian reserve markers based on Bologna and Poseidon criteria.[3] Granulosa cells start producing AMH from the primary follicle stage, reaching peak expression during the secondary follicle stage. The synthesis decreases as the follicle matures, continuing through to the preovulatory stage. In women, serum AMH levels remain relatively steady during infancy, childhood, puberty, and the initial phases of adulthood. However, there is a gradual decrease starting from the fourth decade of life, eventually becoming undetectable a few years prior to menopause. [4,5]

FSH has a crucial role in the development and control of the male and female reproductive systems, exerting its effects through FSHR, primarily found in granulosa and Sertoli cells. In females, FSH stimulates the growth and maturation of follicles and plays a role in LH-induced ovulation and luteinization.[4]

This research aims to assess ovarian reserve in poorly responsive mouse based on AMH and FSH serum levels collected from peripheral (ROB), and central (heart), also from ovarian tissue.

METHODS

The research was conducted from March 2022 to May 2023 at the Indonesia Medical Education and Research Institute (IMERI) within the Animal Research Facility (ARF) Cluster and the Human Reproductive, Fertility, and Family Planning Research (HRIFP) Cluster, as well as at the Integrated Laboratory and Histology Laboratory of the Faculty of Medicine, Universitas Indonesia (FKUI). This research has been approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia, with the ethical clearance letter number: KET-177/UN.2F1/ETIK/ PPM.00.02/2022.

The research design used in this study is an experimental study utilizing a rat model, specifically Sprague-Dawley rats. The short and precisely timed estrous cycle, typically lasting 4–5 days, makes the mouse the preferred mammalian model for human-related research. Additionally, mice have a very brief reproductive age, typically reaching sexual maturity at 4–7 weeks following birth. The reproductive cycle in mice is referred to as the estrous cycle. During estrus, ovarian target tissues are prepared for gestation.[6]

In the experimental setting with mouse, cisplatin will also be administered. Cisplatin is a chemotherapeutic agent used to diminish ovarian reserve in a mouse model. Various doses of cisplatin will be administered to determine the most effective dosage for establishing the model of poorly responsive mouse.[7]

Female Sprague-Dawley rats, aged 8-10 weeks and 28-30 weeks, were utilized in this research. The selected rats exhibited normal estrous cycles lasting 4-7 days, with an average of 5 days. The total number of rats involved in the study was 25. The research was divided into five groups, as follows: Group A: Old-age control group (28–30 weeks); Group B: Cisplatin 1x (administration of cisplatin at 2.5 mg/kgBW/day for 5 days); Group C: Cisplatin 2x (administration of cisplatin at 2.5 mg/kgBW/day for 2 weeks, followed by 1.25 mg/ kgBW/day for 5 days); and Group D: Cisplatin 3x (administration of cisplatin at 2.5 mg/kgBW/

day for 2 weeks, followed by 1.25 mg/kgBW/day for 1 week and 1.25 mg/kgBW/day for 5 days); Group E: Young-age control group (8-10 weeks). Ovaries were collected on the 5th day after cisplatin administration.

Peripheral blood was collected through retro-orbital bleeding (ROB) and central blood from the heart. The volume of blood collected amounted to 8% of the body weight. Safe percentages were estimated at 7.5% every 7 days and 1% every 24 hours. Anesthetized rats had 2 cc of blood drawn from the retro-orbital vein using a heparin-containing capillary tube and 2 cc from the heart using a 2.5 cc syringe needle. The collected blood was placed in serum separator tubes (SST) for centrifugation, and the serum was then collected. AMH and FSH concentrations were quantified using immunoassay methods, such as Enzyme-Linked Immunosorbent Assay (ELISA).[8]

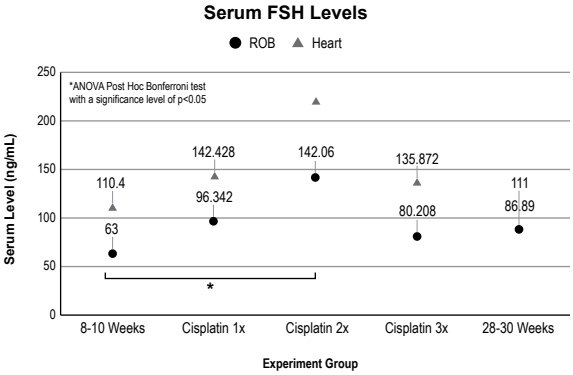
The ovaries of the mice were collected through laparotomy, followed by weighing and histological examination to determine the follicle count using hematoxylin-eosin staining. Follicle counting was performed using one ovary per animal. Paraffin blocks are cut with a microtome to a thickness of 5–6 mm. Follicles were classified based on their histological pattern. They are primordial follicles with one-layer squamous granulosa cells; primer follicles with one-layer cuboid cells; secondary follicles with layers of cuboid cells; antral follicles with layers of cuboid cells; and space with fluid and cumulus granulosa cells. Primordial follicle belongs to the non-growing follicle category, while the primary, secondary, and antral follicle belong to the growing follicle category.[9]

Statistical analysis was conducted using the SPSS vs 20. A significance level of $P<0.05$ was employed to determine statistical significance. ANOVA with subsequent multiple comparisons was applied.

RESULTS

Serum AMH Level in ROB and Heart

The serum AMH levels from ROB in the young age control group, cisplatin 1x group, cisplatin 2x group, cisplatin 3x group, and old age control group were 1151, 1818, 2782.960, 1381.352, and 1544 ng/mL, respectively. The average serum AMH level from ROB was significantly higher in the cisplatin 2x group compared to the other groups. The serum AMH levels from the heart in the young age control group, cisplatin 1x group, cisplatin 2x group, cisplatin 3x group, and old age control group were 2138, 2595.760, 4057.040, 2633.520, and 2062 ng/mL, respectively (figure 1). Similarly, the average concentration of serum AMH in the heart was significantly higher in the cisplatin 2x group compared to the young age control group.



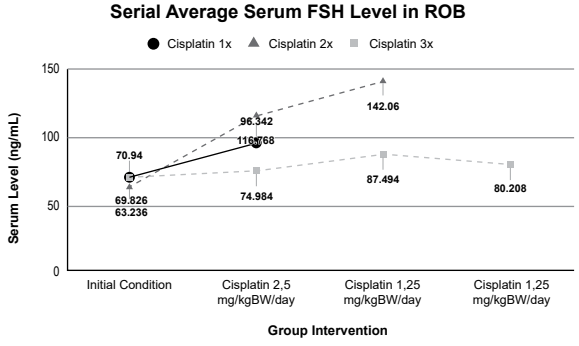


Figure 1. (A) Average Serum FSH Levels for Each Experiment Group.
B Serial Average Serum FSH Levels from Intervention Group: Cisplatin 1x, 2x, and 3x.

Follicle Count

In the follicle count analysis, the group treated with cisplatin 2x exhibited a significantly lower number of live follicles compared to the cisplatin 1x and 3x groups. In the old-age control group, the number of follicles was significantly lower than in the cisplatin 2x group. Conversely, the young-age control group had the highest number of follicles compared to the other groups. Meanwhile, the highest number of atretic follicles was observed in the old age control group, followed sequentially by the cisplatin 3x, cisplatin 2x, cisplatin 1x, and young age control groups

(Figure. 2). The number of non-growing follicles for the young age control group, cisplatin 1x group, cisplatin 2x group, cisplatin 3x group, and the old age control group were 7, 6, 3, 6, and 0, respectively. The number of growing follicles for the young age control group, cisplatin 1x group, cisplatin 2x group, cisplatin 3x group, and the old age control group were 50, 37, 24, 32, and 8, respectively. The number of atresia follicles for the young age control group, cisplatin 1x group, cisplatin 2x group, cisplatin 3x group, and the old age control group were 4, 19, 21, 28, and 30, respectively.

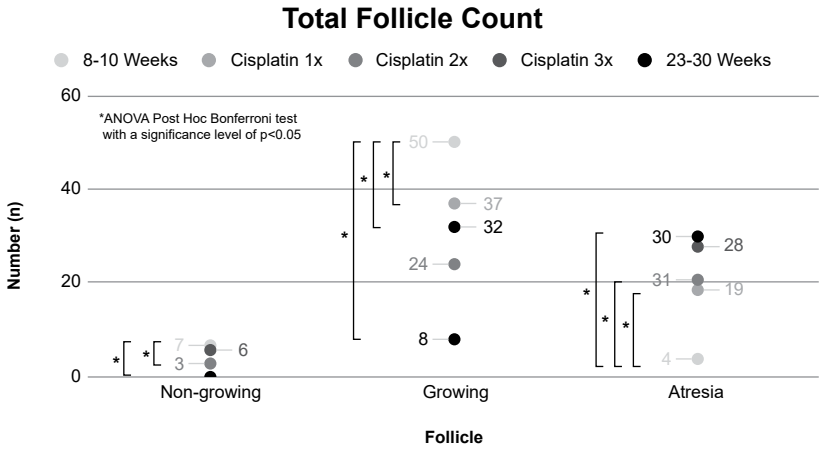


Figure 2. Total Follicle Count For Primordial, Primary, Secondary, Antral, and Atresia Follicle In Each Experimental Group In Mouse Model Study.

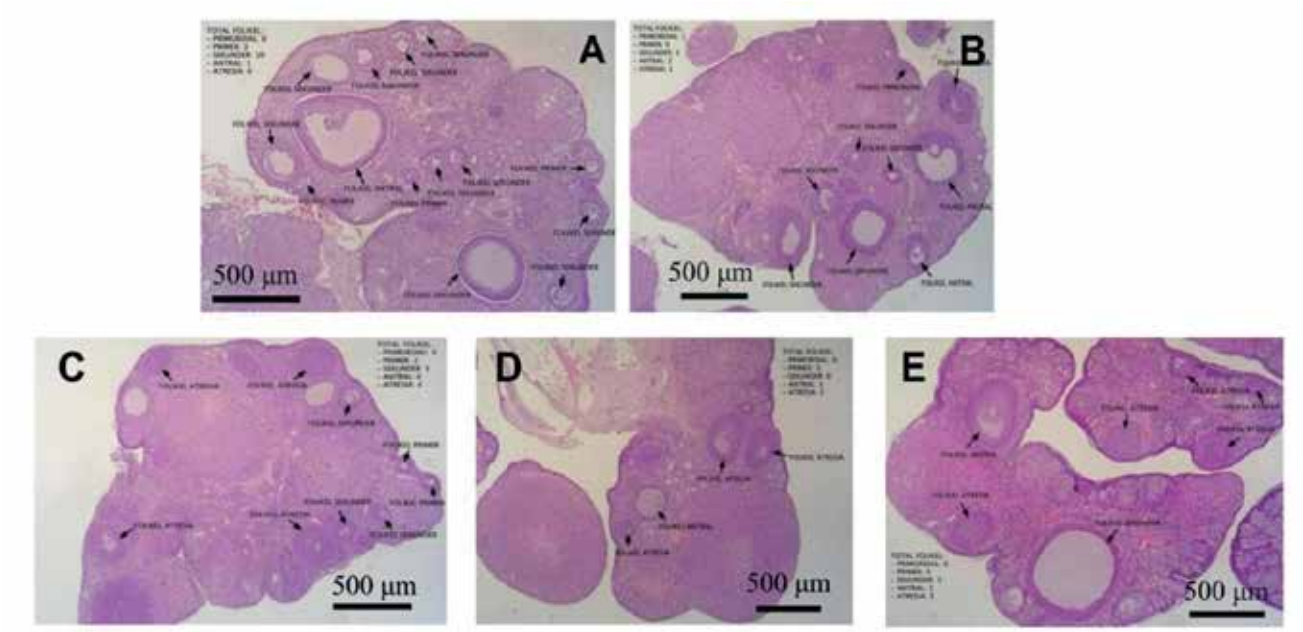


Figure 3. Histological View of Follicle Count for Each Experimental Group With Magnifications x400. Follicle Count Includes Primordial, Primary, Secondary, Antral, and Atresia Follicle. (A) Young age control group. (B) Cisplatin 1x group. (C) Cisplatin 2x group. (D) Cisplatin 3x group. (E) Old age control group.

Ovarian Weight

There were no significant differences in the ovarian weights of the young age control group, the cisplatin 1x group, the cisplatin 2x group, the cisplatin 3x group, and the old age control group. The ovarian weights were 0.555 grams, 0.509 grams, 0.487 grams, 0.387 grams, and 0.191 grams, respectively (Figure. 5).

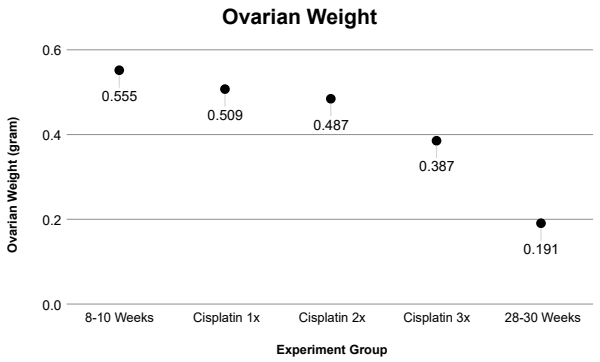


Figure 4. Ovarian Weight In Mouse Model Study.

DISCUSSION

In the selection of control groups, it is evident that the young age control group has a significantly higher number of non-growing and growing follicles compared to the old age control group, indicating the appropriateness of the control group that was used in the study. Cisplatin, as a primary platinum-based chemotherapy agent for ovarian cancer, possesses moderate toxicity that can lead to damage to the ovaries and gonads. Administration of cisplatin induces Premature Ovarian Failure (POF) due to death or accelerated primordial follicle depletion, atresia in growing follicles, damage to stromal tissue, blood vessels, inflammation, and ovarian fibrosis. DNA damage also occurs due to the activation of the P53 apoptosis signaling pathway, oxidative stress, and free radical production.[10]

The administration of cisplatin in the treatment groups reduces the number of follicles in both cisplatin 1x and 2x groups and increases the number of atretic follicles significantly different from the young age control. This finding aligns research that cisplatin and similar compounds induce aneuploidy in mature oocytes correlating with embryonic mortality rates.[11] However, in cisplatin 3x administration, there is an increase in the number of follicles caused by the "burnout" phenomenon. The PI3K/PTEN/Akt pathway brings an end to the dormancy of follicles, directly impacting the oocytes and pre-granulosa cells (pre-GCs) within primordial follicles (PFs). Additionally, it indirectly leads to the breakdown of large follicles. The result of follicle destruction causes a disruption in AMH and diminishes the inhibition of the PF pool. Subsequently, this triggers the activation of PFs in an effort to compensate for the decline in the number of developing follicles. Other studies support these findings, indicating that exposure to cisplatin increases the phosphorylation of proteins in the PTEN/Akt/FOXO3a pathway, including PTEB, Akt, GSK 3, FOXO 3a, and ERK. These changes result in nuclear translocation of FOXO3a, suppressing transcriptional activity, activating PFs, and reducing ovarian reserve. [12-14]

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The evaluation of ovarian reserve was also conducted by examining serum AMH and FSH levels. The research results indicate an increase in AMH and FSH with cisplatin 1x administration, peaking with cisplatin 2x before declining with cisplatin 3x. This condition contradicts the follicle count, where cisplatin 2x was found to be the least compared to cisplatin 1x and 3x. The higher number of follicle count and lower concentration in AMH and FSH in cisplatin 3x was likely due to the burnout phenomenon.

The research also supports that the chemotherapy agent cyclophosphamide (Cy) reduces ovarian follicle reserve by triggering an increase in the PI3K pathway, initiating waves of follicle recruitment and growth, and causing apoptosis of growing follicles within 24 hours of exposure. The study also indicates that AMH expression drops below control concentrations 12 hours after Cy treatment, indicating the loss of growing follicles at that time. However, between 3 and 7 days after treatment, AMH secretion doubles its relative expression and persists for at least 14 days post-treatment. This illustrates an increase in early-growing follicles as a result of follicle activation induced by Cy. The decrease in AMH expression, along with the activation of the PI3K pathway occurring within 24 hours after Cy treatment, combines to create an "irregular growth window" for the dormant PF population. [12,14,15]

The levels of AMH and FSH show significant results with cisplatin 2 times compared to young control and the same pattern, but AMH serves as a more reliable predictor of ovarian reserve compared to FSH because AMH is not influenced by the menstrual cycle, whereas FSH is cycle-dependent. AMH is expressed by growing follicles and can be detected in serum, making it a reliable marker.[16]

Serial blood sampling through the ROB technique and heart blood collection at necropsy yielded similar results. Thus, blood collection via ROB is considered an alternative, less invasive technique for treatment groups requiring serial observations.

CONCLUSION

In the follicle count, the group treated with cisplatin 2x exhibited a significantly lower number of live follicles compared to the cisplatin 1x and 3x groups. The average concentrations of serum AMH and FSH in the ROB and heart were higher in the 2x cisplatin group compared to the other groups. The more cisplatin added the more ovarian reserve reduced and it corresponds to the old age control group. The increase in the follicles count and decrease in serum level in the cisplatin 3x group was due to the burn out phenomenon. Blood collection through the ROB is considered a less invasive alternative technique in the treatment group, requiring serial observation.

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Case Report

Hypertriglyceridemia - Induced Acute Pancreatitis in Pregnancy

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Abstract

Objective: To describe the prompt and successful treatment of an hypertriglyceridemia-induced acute prancreatitis in pregnancy complicated by severe preeclampsia case in a tertiary-level hospital in Indonesia.

Methods: A Case report. A 33-year-old woman, G3P2A0 at 32/33 weeks of gestation, presented with shortness of breath following severe heartburn, nausea, and fever. She had been experiencing constant thirst and frequent urination. Her level of consciousness was decreased (GCS E2V3M4), and she exhibited high blood pressure and tachycardia. There was no history of high blood pressure during her routine antenatal care. Laboratory tests revealed a leukocyte count of 22,670/µL, a random blood sugar level of 713 mg/dL, severe metabolic acidosis on blood gas analysis, an amylase level of 1,004.8 U/L, a lipase level of 899.4 U/L, and triglycerides at 789 mg/dL. An abdominal CT scan with contrast confirmed acute pancreatitis. Given her poor general condition, she was sedated and intubated. The termination of her pregnancy was postponed to focus on stabilizing her condition in intensive care.

Discussion: In pregnant patients presenting with severe heartburn and no prior history of hypertension, acute pancreatitis should be considered as a potential diagnosis. In the absence of alcohol abuse risk factors, hypertriglyceridemia should be investigated as a probable cause.

Conclusion: Pregnant patients presenting with symptoms of shortness of breath, severe heartburn, along with hypertriglyceridemia should be considered for acute pancreatitis as a differential diagnosis.

Keywords: Acute Pancreatitis, Hypertriglyceridemia, Pregnancy, Preeclampsia.

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INTRODUCTION

Pregnancy is characterized by the anticipation of a new life while also harboring concerns for its subsequent growth. It is a well-established fact that delaying the age at which women decide to have children has significant repercussions for both the mother and the baby[1].The pancreas is an elongated and planar gland situated in the upper abdominal region. The pancreas synthesizes enzymes and hormones that facilitate digestion and control glucose metabolism[2]. Pancreatitis refers to a condition characterized by inflammation of the pancreas. This inflammation can manifest as either acute, characterized by a quick start, or chronic, stemming from a previous bout of pancreatic inflammation that ultimately leads to pancreatic dysfunction[3]. Acute pancreatitis is an inflammatory condition that mostly affects the exocrine portion of the pancreas. It is characterized by severe stomach pain and the malfunction of several organs, leading to pancreatic necrosis and prolonged organ failure. The death incidence ranges from 1% to 5%. The illness has a worldwide prevalence of 30–40 cases per 100,000 individuals annually[4].

Acute pancreatitis in pregnancy (APIP) is a rare case, with an estimated incidence between 1/1000 and 1/10,000 of the pregnancies[5]. Most cases of APIP occur in the third trimester (50-52%) of pregnancy or early after delivery (38%)[6]. The incidence of pancreatic illness during pregnancy has increased significantly in the past 2–3 decades[1]. APIP has a sudden and severe beginning and typically poses challenges in terms of diagnosis and treatment. Based on a research analysis, APIP is more hazardous for the fetus compared to the mother. The incidence of maternal death caused by pancreatitis is documented at 37%, while the fetal mortality rate can reach up to 60%. However, recent advancements in diagnostic and treatment options have led to a decrease in maternal and fetal mortality[3,6,7]. Hypertriglyceridemia (4%-10%) is known as the third most common cause of acute pancreatitis after gallstones (66%) and alcohol abuse (12%)[8]. In one study it was reported that hypertriglyceridemia-induced pancreatitis (HTGP) reached up to 56% of APIP cases[9]. Preeclampsia/eclampsia that occurs with or aggravated by acute pancreatitis is a rare case and there are no more than two cases in any reported cases[10]. This case report is to describe the prompt and successful treatment of an hypertriglyceridemia-induced acute prancreatitis in pregnancy complicated by severe preeclampsia case in a tertiary-level hospital in Indonesia. Where this case report of severe preeclampsia is a complication of acute pancreatitis in pregnancy, which is different from most previously published journals.

METHODS

A 33-year-old woman, G3P2A0 at 32/33 weeks of gestation, was referred from a hospital with complaints of shortness of breath for six hours before admission. Prior to the shortness of breath, the patient experienced severe heartburn radiating to the back, which did not improve with self-medication at home, and was accompanied by nausea and fever since the previous day. The patient did not experience vomiting. According to family information, the patient had been constantly thirsty and frequently waking up to urinate since the previous day. The patient had a history of asthma (last recurrence in 2012) and was given salbutamol nebulization at the hospital, which did not improve her condition and instead worsened it. Due to the need for further treatment, the patient was referred. Upon admission, the patient had a GCS score of 456, which later decreased to GCS E2V3M4. She appeared short of breath with a respiratory rate of 36-44 breaths per minute, blood pressure of 170/110 mmHg, pulse rate of 134-140 beats per minute, temperature of 38.4°C, and SpO2 of 100% (with O2 NRM 10 L/min). No additional breath sounds were detected in the heart or lung fields. The patient had no history of high blood pressure during routine pregnancy check-ups. High blood pressure was only discovered when the patient began to complain of shortness of breath. From the patient's obstetric status, the height of the uterine fundus was 26 cm, with head presentation, no contractions, and a fetal heart rate (FHR) of 110-115 beats per minute. Laboratory results showed leukocytes at 22,670/µL, random blood sugar at 713 mg/dL, and severe metabolic acidosis (pH 6.944, pO2 148, pCO2 9.3, HCO3 5.5, BE -28.5, SO2 97%) on blood gas analysis. Previous hospital laboratory results indicated proteinuria and bacteria (+) in the urine. During antenatal care (ANC), the patient never had her blood sugar checked, but according to her husband, she had her blood sugar checked in 2020, before becoming pregnant, due to complaints of weakness. The results showed a random blood sugar level of >200 mg/dL. However, the patient only reduced her intake of sweets and did not pursue further examination at a health facility.

CASE

In this case, the patient presented in poor general condition with respiratory failure, loss of consciousness (GCS E2A3M4), and severe metabolic acidosis. She was sedated and intubated by the Emergency Medicine team. The termination of the pregnancy was postponed to prioritize stabilizing the mother's condition. The patient received fluid rehydration therapy, a sodium bicarbonate infusion, antibiotics, and insulin therapy via an insulin pump. She was treated in the ICU.

By the following morning, the patient was conscious and no longer sedated, had been extubated since dawn, with a blood pressure of 188/94 mmHg and a respiratory rate of 22 breaths per minute. Obstetric status revealed a good fetal heart rate (FHR) of 153-155 beats per minute. Further laboratory examination in the ICU showed a random blood sugar level of 319 mg/dL, elevated pancreatic enzymes with amylase at 1,004.8 U/L and lipase at 899.4 U/L, and elevated

triglycerides at 789 mg/dL. Suspecting acute pancreatitis, an upper and lower abdominal ultrasound or a CT scan with contrast was planned post-delivery.

With the patient's general condition improved and the fetus stable, we proceeded with a caesarean section to terminate the pregnancy. After the delivery, a contrast-enhanced abdominal CT scan confirmed acute pancreatitis. Postpartum, the patient continued on insulin pump therapy and antibiotics. During her 11-day hospital stay, the patient's condition gradually improved. Final laboratory results showed pancreatic amylase at 42.6 U/L and lipase at 105 U/L. The patient was discharged without complaints, along with a healthy baby.

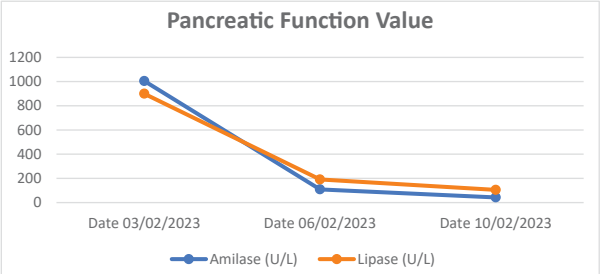

Figure 1. Changes in pancreatic function values patients during hospitalized

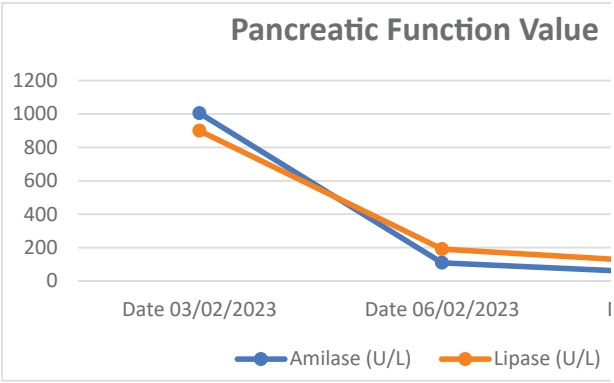

Figure 2. The results of abdominal CT Scan with contrast are consistent with acute pancreatitis

DISCUSSION

Acute pancreatitis during pregnancy is an uncommon occurrence. While uncommon, it is important to acknowledge that the likelihood of problems is twice as high in pregnant women compared to non-pregnant women. Pancreatitis during pregnancy can manifest in any trimester, but it is uncommon in the first 6 months (12%). It predominantly occurs in the third trimester (50–52%) or shortly after birth (38%)[11,12]. This aligns with the events of the case, which took place during the third trimester at around 32–33 weeks of gestation.

According to the updated Atlanta's categorization of acute pancreatitis, the diagnosis of acute pancreatitis necessitates the presence of at least two out of the following three characteristics; The abdominal discomfort is indicative of acute pancreatitis, characterized by continuous, intense pain in the upper abdomen that commonly spreads to the back; the activity of serum lipase (or amylase) is elevated to at least three times the normal limit; and acute pancreatitis characteristics identified using an abdominal CT scan, abdominal MRI, or abdominal ultrasound examination[13]. Although lipase and amylase tests are valuable for detecting acute pancreatitis, repeatedly measuring them in individuals with the condition is not helpful for forecasting the prognosis and severity of the disease. The rise in lipase levels has a more prolonged duration in comparison to the increase in serum amylase levels. Consequently, lipase is highly beneficial in patients who seek medical attention more than 24 hours after the start of discomfort[2]. Mild acute pancreatitis is defined by the absence of organ dysfunction and the absence of both local and systemic consequences. Patients experiencing organ failure that lasts less than 48 hours and/or consequences that affect a specific area or the entire body but do not result in ongoing organ failure are categorized as having moderately severe pancreatitis. Patients who have had organ failure for more than 48 hours are classified as having severe pancreatitis. Organ failure was categorized based on the modified Marshall score method for assessing organ dysfunction[2,13,14]. The patient mentioned can be definitively diagnosed with acute pancreatitis. This conclusion is based on several factors: the patient has been experiencing severe heartburn since the day before being referred; a sudden increase in blood sugar is found as a sign of pancreatic organ failure, there is an elevation in serum amylase and lipase activity (specifically, amylase values of 1,004.8 U/L and lipase values of 899.4 U/L); and the results of the abdominal CT scan reveal the presence of characteristics consistent with acute pancreatitis. This patient may be classified as having moderate-to-severe acute pancreatitis based on the severity. The PaO2/fiO2 ratio, which measures the oxygen levels in the blood, yielded a result of 185.

Table 1. Modified Marshall Scoring System for Organ Failure[14]

Organ System	Score				
Respiratory (PaO_2/FiO_2)	**0** >400	**1** 301-400	**2** 201-300	**3** 101-200	**4** ≤101
Rena l* (serum creatinine, µmol/l)	≤134	134-169	170-310	311-439	>439
(serum creatinine, mg/dl)	<1.4	1.4-1.8	1.9-3.6	3.6-4.9	>4.9
Cardiovascular (systolic blood pressure, mmHg)†	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH <7.3	<90, pH <7.2
For non-ventilated patient, the FiO2 can be estimated from below :					
Supplemental oxygen (l/min)	FiO_2 (%)				
Room Air	21				
2	25				
4	30				
6-8	40				
9-10	50				

A score of 2 or more in any sytem defines the precense of organ failure
*A score for patients with pre-existing chronic renal failure depends on the further deterioration of baseline renal function. No formal correction exists for a baseline serum creatine ≥ 134 µmol/l or ≥ 1.4 mg/dl
† off inotropic support

Hypertriglyceridemia is defined as a fasting serum triglyceride levels above 150 mg/dL (1.7 mmol/L)[9]. In a typical pregnancy, there are specific adjustments in the way lipids are processed. This involves an increase in the production of lipoproteins, which is caused by higher levels of estrogen. Additionally, there is a decrease in the activity of lipoprotein lipase owing to increased insulin resistance. The purpose of these modifications is to guarantee the placenta's requirements and the glucose and lipid demands of the developing fetus. This involves enhancing glucose production, synthesis progesterone, and promoting lipogenesis while simultaneously decreasing lipolysis. The elevation in estrogen levels and subsequent enhancement of lipoprotein production contribute to an elevation in triglyceride levels. Additionally, the decrease in lipoprotein lipase activity hinders the removal of triglycerides, leading to elevated triglyceride levels in the bloodstream[6,11,15–17]. Triglyceride levels reach their highest point during the third trimester of pregnancy, often increasing to 2-4 times higher than normal values. However, this rise very rarely goes over 300 mg/dL (16.7 mmol/L), which is not enough to trigger severe pancreatitis. Acute pancreatitis is more likely to develop when triglyceride levels are above 500 mg/dL; however, it most commonly happens when triglyceride levels surpass 1000 mg/dL[1,6]. The incidence of hypertriglyceridemia-induced pancreatitis (HTGP) has been documented to be as high as 22 percent; however, it is often believed to account for 5% of all instances of acute pancreatitis and up to 56% of cases of acute pancreatitis during pregnancy[9]. One of the complications of hypertiglyceridemia in pregnancy is hyper-viscosity syndrome, which is preeclampsia and an increased risk of hyperlipoproteinemia later in life. Hypertriglyceridemia has a significant impact on the pathogenesis of pregnancy-induced preeclampsia and is associated with an increase in lipid peroxidation products that act as a dysfunction of endothelial oxidative stress.[16-18]. In this instance, there was no record of alcohol misuse. The CT scan results revealed no abnormalities in the gallbladder or its ducts. The patient's triglyceride level was measured at 789 mg/dL, which the author considers to be a significant contributing factor in the development of acute pancreatitis in this case.

Severe preeclampsia can exacerbate the onset of acute pancreatitis. Severe preeclampsia is linked to microvascular alterations, such as arteriole spasms, microthrombosis, DIC (disseminated intravascular coagulation), and vasculitis, which impair the functioning of several organs, including the pancreas. The presence of microvascular abnormalities in pregnant women with eclampsia is believed to be a contributing

factor to the development of acute pancreatitis. In addition, severe preeclampsia is linked to higher levels of inflammatory mediators or a higher sensitivity to these mediators. These can potentially cause or start inflammation of the pancreatic gland tissue, which can lead to acute pancreatitis or its worsening. The presence of simultaneous hyperlipidemia, cholestitis, or cholelithiasis increases the likelihood of developing acute pancreatitis[10]. After doing an examination, we found that the individual had high blood pressure readings of 170/110, and protein was detected in a thorough urine analysis. Nevertheless, there was no documentation of elevated blood pressure throughout prenatal care. The patient initially had dyspnea, which was then accompanied by intense heartburn, nausea, and a variable body temperature, leading to the detection of hypertension. During the patient's hospitalization, there is a gradual decline in blood pressure, which corresponds to a drop in amylase levels or an improvement in acute pancreatitis. Hence, it may be inferred that the acute pancreatitis in this patient led to the onset of severe preeclampsia, which was a result of hypertriglyceridemia. The patients recovery from acute pancreatitis and a decline in blood pressure were indicators of this. This demonstrates that the sequence in this case differs from most others, with acute preeclampsia occurring after acute pancreatitis, while in the case series, acute pancreatitis was a complication that resulted from preeclampsia.

Hypertriglyceridemia-induced acute pancreatitis during pregnancy is a rare illness, and there is less scientific evidence available to inform its treatment. Efficient management depends on a varied care team of professionals with proficiency in other fields, in addition to the physicians' competence[19]. In this instance, the author engaged a multidisciplinary team consisting of the author as an obstetrics specialist, along with colleagues specialising in endocrinology, anesthesia, and stomach surgery.

The initial management of acute pancreatitis during pregnancy does not significantly differ from the management of acute pancreatitis in non-pregnant individuals. The primary therapeutic measures include administering oxygen, restoring fluid levels, managing discomfort, and discontinuing oral intake (bowel rest) to inhibit the exocrine activity of the pancreas, thereby averting self-digestion by the pancreas. Upon the identification of hypertriglyceridemia, treatment should be initiated with the objective of decreasing triglyceride levels[11,19]. The main therapy used in this case is fluid rehydration with normal saline (NS) and insulin pump, which is adjusted to the patient's sugar level. Elevated blood glucose in acute pancreatitis is an indication of more severe acute pancreatitis. This can occur due to a complex endocrine insufficiency. This can lead to a decrease in insulin production, a rise in insulin resistance, or a mix of both[3,4].

Insulin increases lipoprotein lipase activity, thereby decreasing the production of Very Low Density Lipoprotein (VLDL) and also reducing serum triglycerides. There is little evidence that insulin is superior to the NPO diet (nil per os/ nothing by mouth) in reducing serum triglycerides in the treatment of hypertriglyceridemia-induced acute pancreatitis[19]. In this scenario, insulin is administered at an initial rate of 5 U/hour, with the possibility of adjusting the dosage up or down based on the patient's blood glucose level. Regrettably, we failed to verify the serum triglyceride levels again after correcting them with insulin in this particular instance.

The case studies have examined the conservative strategy of using a low-lipid diet together with omega-3 fatty acid supplementation. Omega-3 fatty acids are recognized for their ability to decrease the secretion of triglycerides in the liver and enhance the activity of lipoprotein lipase. Omega-3 fatty acids have fewer negative effects compared to other medications that decrease triglyceride levels, such as fibrates, statins, and nicotinic acid. This makes omega-3 fatty acids the preferable therapeutic choice for managing hypertriglyceridemia during pregnancy. There have been no documented adverse effects associated with the use of Supplement (this patient has omacor), which contains omega-3 fatty acids. However, there is one case study that described instances of diarrhea and respiratory distress syndrome in neonates. Another study found no correlation between preterm birth and the administration of omega-3 fatty acids during pregnancy[8]. Nevertheless, the patients we now serve have not been offered this therapeutic alternative. However, in the future, using this therapy as a potential strategy for treating acute pancreatitis in pregnancy due to hypertriglyceridemia might be considered.

CONCLUSION

Pregnant patients presenting with symptoms of shortness of breath, severe heartburn not relieved by treatment, a history of fever, a sudden increase in blood sugar, and hypertriglyceridemia should be considered for acute pancreatitis as a differential diagnosis. Rapid identification and appropriate treatment can reduce maternal and fetal mortality.

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Case Report

Pregnancy after Succesful Fallopian Tube Recanalization

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Abstract

Objective: To report a pregnancy that ensued following the successful recanalization of a previously sterilized fallopian tube. The novel aspect of this report is its demonstration of a successful intrauterine pregnancy post-recanalization, despite a prior ectopic pregnancy resulting from tubal sterilization.

Methods: Case report

Case: A 35-year-old woman successfully conceived after the recanalization of a previously sterilized fallopian tube. It is noteworthy that she had previously experienced an ectopic pregnancy due to the tubal sterilization procedure.

Conclusion: This case study highlights the potential for successful pregnancy following fallopian tube recanalization, even after an ectopic pregnancy caused by a prior sterilization procedure. This report underscores the complexity of reproductive outcomes in these scenarios.

Keywords: fallopian tube recanalization, pregnancy, tube sterilization.

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INTRODUCTION

Tubal sterilization is a commonly chosen method of permanent contraception among women of childbearing age. The significance of informed consent in this procedure cannot be overstated. It is vital to underscore that tubal sterilization is an irreversible operation and not designed for reversal.[1,2] The procedure involves the surgical cutting, tying, or blocking of the fallopian tubes to prevent pregnancy. By hindering the ascent of sperm through the fallopian tubes to the egg and obstructing the passage of eggs from the ovaries through the tubes, conception is effectively inhibited. The cumulative 10-year failure rate of tubal sterilization ranges from 7.5 to 18.5 pregnancies per 1,000 sterilization procedures[3,4]

Fallopian tube recanalization (FTR) is a proven and secure procedure tailored for women experiencing fallopian tube obstruction. Previous studies have shown that recanalization after tubal sterilization occurs at a mean interval of 6.10 years (SD 4.0; range 1–16). The main reason for seeking reversal of sterilization was the death (65.5%) or disability (6.9%) of one or more children.[5] In the remaining 27.6%, a second marriage was the reason for reversal of sterilization. The technique of fallopian tube recanalization was introduced in 1987.[6] Interventional tubal recanalization or fallopian tube recanalization (FTR) is a highly effective procedure for treating proximal tubal obstruction with technical success rates as high as 90%, with intrauterine pregnancy rates of 20-60% and 50% of pregnancies occurring within one year after recanalization.[7] The aim of this case is to demonstrate the success of a woman who achieved spontaneous intrauterine pregnancies following the Pomeroy technique of tubal sterilization, due to a subsequent tubal recanalization.

CASE

A 35-year-old woman presented to the obstetrics and gynecology outpatient clinic at YPK Hospital, Jakarta, Indonesia, seeking to conceive after a 5-year history of tubal sterilization performed using the Pomeroy technique. The patient has three children, with previous Cesarean sections conducted in 2012, 2014, and 2016 at a private hospital in Central Java. Shortly after the sterilization, the patient divorced and subsequently remarried.

Prior to recanalization, the patient underwent HSG (hystero-salphingo-graphy) examination and showed nonvisualized both fallopian tubes and the levo-retroflexed position of the uterus. Isthmi-Isthmica recanalization through laparotomy surgery will be carried out in June 2021 and both tubes are declared patent. In this patient, laparotomy was performed due to the limitations of laparoscopic equipment. The patient was asked by the doctor to do a post-recanalization HSG, but the patient did not do it.

On April 20th, 2022 she complained of acute abdominal pain not accompanied by vaginal bleeding. The patient at that time did not realize that she was pregnant. The patient at that time was at work and experienced severe abdominal pain, then the patient was taken to Hermina Daan Mogot Jakarta Hospital and an ultrasound was performed with the result of a ruptured ectopic pregnancy. The patient underwent an emergency salpingectomy laparotomy in one of the fallopian tubes and the patient was discharged in good condition.

In February 2023, she revisited the obstetrics and gynecology outpatient clinic with the chief complaint of amenorrhea with a positive result of home pregnancy test. An ultrasound confirmed the pregnancy, revealing a gestational sac and fetal heart rate. The patient gave birth to a healthy baby girl by cesarean section on October 26th, 2023.

DISCUSSION

Tubal sterilization is a common method of contraception preferred by women of childbearing age who desire permanent contraception. The combined cumulative failure rate for all sterilization methods is 18.5 per 1,000, depending on the technique used. In this patient, tubal sterilization was performed after a cesarean delivery, with the abdomen already open. The Pomoroy technique was used for sterilization, which is known for its potential for recanalization. During the Pomeroy procedure, the mid-isthmic portion of the Fallopian tube is elevated and folded at the midpoint. One or two rapidly absorbable sutures are tied around the double thickness of the tube, and the folded portion is then sharply excised.[8]

Informed consent for tubal sterilization is of paramount importance and must explicitly state that the procedure is permanent and not intended to be reversible. It is crucial to discuss the potential for regret and the associated risk factors, which include young age at the time of sterilization (under 30 years), low parity, sterilization performed immediately postpartum, and changes in marital status such as divorce or remarriage. Young age at the time of sterilization is the most significant predictor of regret. In this particular case, the patient reported that she had not received informed consent, although her family had provided it on her behalf. Additionally, the patient experienced divorce and subsequent remarriage, leading her to request recanalization.[3]

In this patient, prior to recanalization, a hysterosalpingography (HSG) examination was performed, which revealed no contrast filling in the right and left fallopian tubes, indicating an obstruction at the isthmus of both tubes.

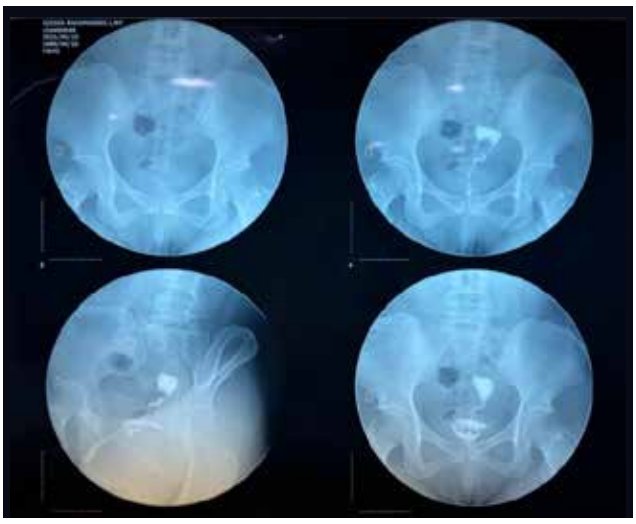

Figure 1. HSG examination was performed before recanalization which showed no visible picture of contrast filling into the right and left fallopian tubes according to the obstruction in the projection of the isthmus of both tubes

Fallopian tube recanalization (FTR) is a safe and effective procedure for women with fallopian tube obstruction caused by tubal sterilization. The current application of FTR, first described in the

literature, can be performed via laparotomy or laparoscopic surgery. In this patient, recanalization was performed by laparotomy using isthmo-isthmic recanalization at the Pomeroy sterilization site. Initially, a catheter was inserted through the cervix into the uterus for a methylene blue test. After identifying the fallopian tube, any adhesions were released, and excision was carried out at the proximal end of the tube until a healthy lumen was found, confirmed by the methylene blue test. The distal end of the tube was then excised until a healthy lumen was identified with the help of a tubal sound inserted from the fimbrial end. The anatomy of a healthy tube segment was clearly visualized with methylene blue drops, allowing the lumen with cilia, tunica muscularis, and tunica serosa to be accurately identified.

Following this, the tunica muscularis is sutured at the 6 o'clock and 12 o'clock positions using monofilament thread number 7, as additional stitches can lead to contracture. Next, the two tube fragments are closed with several stitches in the tunica serosa. The procedure concludes with a methylene blue test to assess tubal patency. If there is a leak in the recanalization area but the methylene blue reaches the fimbrial end, the tube is considered patent. The same technique and procedure are then performed on the contralateral tube.

Interventional tubal recanalization, also known as fallopian tube recanalization (FTR), is a highly effective procedure for treating proximal tubal obstruction. It boasts technical success rates as high as 90%, with intrauterine pregnancy rates ranging from 20% to 60%, and 50% of pregnancies occurring within one year after recanalization.[9,10]

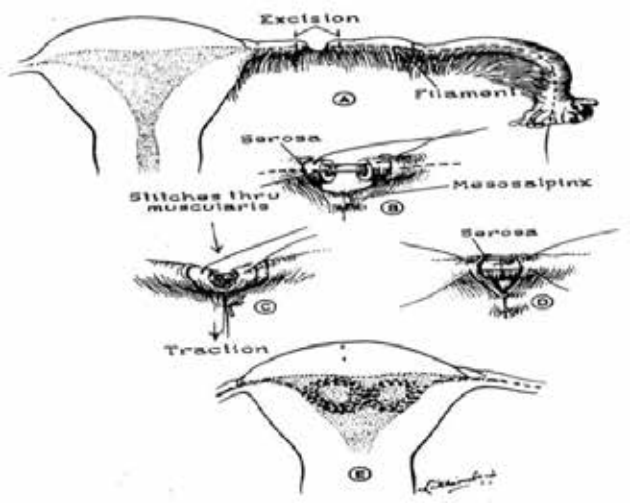

Figure 2. Isthmi-isthmica Procedure

FTR complication rates are low, with studies showing tubal perforation, infection, and ectopic pregnancy occurring in 1% to 9% of cases. This patient experienced an ectopic pregnancy 10 months after fallopian tube recanalization, necessitating a laparotomy salpingectomy. Previous studies have reported ectopic pregnancy rates ranging from 0% to 13%. The occurrence of ectopic pregnancies after FTR may be attributed to peritubal adhesions, which are not visible during FTR but can be easily identified during diagnostic laparoscopy.[11]

Although the risk of ectopic pregnancy is higher in patients who have undergone FTR, this risk is primarily associated with the pre-existing tubal abnormalities rather than the procedure itself. Therefore, FTR is considered a therapeutically valuable and effective method for managing fallopian tube obstruction.[6]

The patient achieved a spontaneous pregnancy 10 months following fallopian tube recanalization, but experienced an ectopic pregnancy despite the methylene blue test confirming tubal patency. One year later, the patient had another spontaneous pregnancy. She has not encountered infertility for over 5 years. Data indicate that spontaneous pregnancy rates are higher in individuals with a shorter history of infertility (<5 years) compared to those with a longer history (>5 years) (68.4% vs. 31.6%). A prolonged duration of infertility may be associated with chronic tubal inflammation, potentially damaging the tubal mucosa and cilia. These findings align with the reported outcomes of fallopian tube recanalization (FTR), which shows intrauterine pregnancy rates ranging from 20% to 60%, with 50% of pregnancies occurring within one year following the procedure.[9,10]

CONCLUSIONS

In conclusion, tubal sterilization is a widely utilized contraceptive method favored by women of childbearing age seeking permanent birth control. This case highlights the successful outcome of a woman who achieved spontaneous intrauterine pregnancies following a Pomeroy technique tubal sterilization, due to subsequent tubal recanalization.

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Systematic Review

Expression of Yap Signaling Hippo Pathway in Cervical Pre-cancerous Lesions and Cervical Cancer

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Abstract

Objective: To determine the expression of YAP in cervical pre-cancerous and cervical cancer lesions.

Methods: Researchers systematically searched five databases using the checklist for Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guideline and Newcastle-Ottawa Scale (NOS).. Inclusion criteria were the original study of YAP expression in cervical pre-cancerous lesions and cervical cancer, observational and experimental study, and using immunohistochemical techniques. The study protocol was registered in the PROSPERO database of systematic review (IDCRD42023407469).

Results: The data search in this study followed the PRISMA Guideline, which includes phases of identification, screening, and inclusion of studies. Initially, 245 articles were identified across five databases: Pubmed (105), ScienceDirect (8), Scopus (29), Web of Science (26), and ProQuest (77). After removing duplicates, 157 studies remained. During the initial screening, 142 studies were excluded, leaving 15 studies for further evaluation. These were assessed based on the use of immunohistochemistry staining for YAP expression and staining result. Subsequently, ten studies were excluded for either not using immunohistochsmistry or lacking staining result, resulting in five studdies selected for qualitative analysis. These five studies were evaluated using the New Ottawa Scale, as detailed in Table 1, and their YAP Expression characteristics are summarized in Table 2.

Conclusion: This systematic review showed that YAP expression at all levels ranging from normal tissue, cervical intraepithelial neoplasia, squamous cell carcinoma, and adenocarcinoma had increased expression in the cytoplasm or cell nucleus following the development of cervical cancer and tumorigenesis influenced by intra-tumor heterogeneity for YAP expression. YAP is expressed in the cytoplasm and nucleus, with different functions. YAP expression in these two sites Excessive YAP expression will trigger epithelial changes into mesenchyme which also plays a role in cancer development. This YAP expression also correlates with HPV, in which YAP levels will be maintained and increased.

Keywords: cervical cancer, cervical pre-cancerous lesions, YAP expression.

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INTRODUCTION

Cancer is a medical condition that initiates when regular cells transform into irregular cells, proliferating excessively and surpassing their typical boundaries within the body. This ailment can originate in nearly any body organ or tissue and has the potential to propagate to other parts of the body. The final phase of the cancer progression involves metastases, which is the primary cause of cancer-related deaths.[1]. Cervical cancer, a significant health concern predominantly affecting women, is primarily linked to Human Papillomavirus (HPV) infection. While most HPV infections are harmless and self-limiting, persistent infection by high-risk HPV strains, notably type 16, can escalate to the development of various cancers in the cervix, vagina, anal region, penis, and oropharynx. Besides viral infection, genetic mutations and

epigenetic modifications also play a crucial role in the pathogenesis of cervical cancer [2].

In 2018, the number of new cases of cervical cancer in the world was 570,000, and the number of deaths caused by cervical cancer was 311,000. Cervical cancer is the second leading disease in incidence and mortality after breast cancer. In Indonesia, cervical cancer ranks second out of the 35 most common cancers, with 9.2% of new cases in 2018, and ranks third with 9.0% of deaths[3,4].

The approach to manage with cancer depends on its stage and how far it has spread within the body. Initial strategies for managing cancer involve surgical interventions (such as conization, different types of hysterectomy, and lymph node removal) or a combination of radiation and chemotherapy[5]. Nevertheless, these treatments come with various unwanted effects. Recent studies have delved into alternative methods for managing cancer growth and inducing cancer cell death through the Hippo Signaling Pathway. This pathway, initially identified in fruit flies and later found in mammals, involves key molecules like Hippo, Salvador, Warts, Mats, Yorkie, and Scalloped in fruit flies, and Mst1-2, Sav1/WW45, Lats 1-2, MOBKL 1A-B, YAP, TAZ, TEAD1-4 in humans[6]. YAP and TAZ, critical components in this process, assume a vital role as co-activators during hippo signalling. They enter the cell's nucleus and bind with TEAD, prompting the activation of genes that encourage growth. This mechanism also supports the regeneration of organs following injury. When YAP and TAZ are excessively activated due to abnormalities in the Hippo pathway or their overexpression, the risk of cancer development is heightened[7]. Leveraging the Hippo Pathway signal could offer a promising alternative for managing cancer. This research aims to evaluate the expression levels of YAP in pre-cancerous cervical lesions and cervical cancer through a systematic review, incorporating a comprehensive literature search across major scientific databases.

METHODS

This systematic review was conducted and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. An electronic search was conducted using the keywords: (YAP Expression) AND ((Cervical Cancer) OR (Cervical Lesion) OR (Cervical Carcinoma)) with a journal time range from 2010 to 2022. The databases used in the literature search in this study are Pubmed, Science Direct, Scopus, Web of Science, and Proquest.

Inclusion criteria for this study included; Cervical pre-cancerous lesions in the form of cervical intraepithelial neoplasia based on WHO classification; Cervical cancer with squamous cell carcinoma and adenocarcinoma types based on FIGO classification; Observational and experimental studies; and Research that is an original study, Staining with immunohistochemical techniques. Meanwhile, the exclusion criteria in this study include Other cancers other than cervical cancer were found; Observations with western blot analysis, Quantitative Real-Time PCR, Immunofluorescent, and Haemotoxyline staining; The results observed are not related to YAP expression; not available in full-text. The PICO (Patients, Index, Comparability, Objective) approach was used in this study. Patients, Patients with cervical pre-cancerous lesions and cervical cancer; Index, YAP expression; Comparison, Staging criteria for cervical cancer; Outcome, Percentage of YAP expression in cervical pre-cancerous lesions and cervical cancer. Literature that has been filtered based on the elimination of duplicated literature and inclusion and exclusion criteria will be processed in two stages: selection based on titles and abstracts that do not match the specified keywords or PICO and cannot be accessed. The second stage is reading full-text articles that meet the inclusion and exclusion criteria. Literature that meets the requirements is called eligible. Eligible literature will be assessed using the Newcastle Ottawa Scale.

The authors extracted data from all the retrieved studies and evaluated their quality using full-text articles. If there are differences of opinion, researchers will check and discuss them with each other. The authors, the year of the study, study location, study design, population characteristics, the number of samples, the age of the samples, diagnostic method, and the expression of YAP in the study were among the data picked.

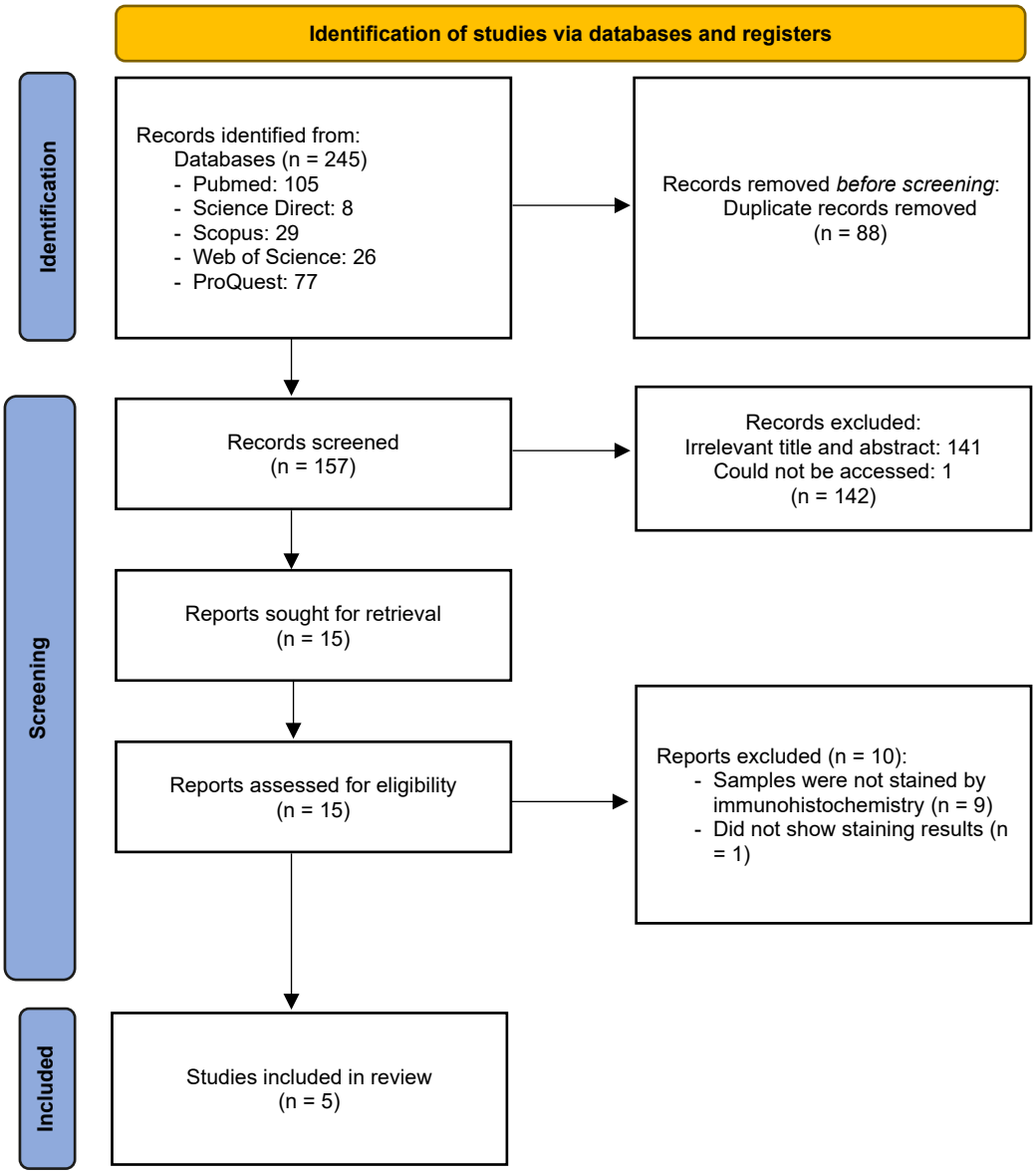

Figure 1. PRISMA 2020 flow diagram.

RESULTS

The data search in this study followed the PRISMA guidelines, as shown in Figure 1. This process is divided into three phases: identification, screening, and inclusion of studies. During the identification phase, researchers searched for articles across five different databases: PubMed, ScienceDirect, Scopus, Web of Science, and ProQuest, using automation tools. The search yielded 105 studies from PubMed, eight from ScienceDirect, 29 from Scopus, 26 from Web of Science, and 77 from ProQuest, totaling 245 articles. Duplicate studies were removed before proceeding to the screening phase, resulting in the exclusion of 88 studies.

At the initial screening stage, 142 studies were excluded. So there are 15 studies to be continued to the next step. In the second stage, the reading of the entire text focused on the staining method using the Immunohistochemical Technique, YAP expression, and the staining results. From the results of this second stage, ten studies were excluded, with details of 9 studies not stained with immunohistochemistry, and 1 study did not show staining results, so five studies would be used as sample material for this study.

Table 1. New ottawa scale.

	Liu et al. **[8]**	Xiao et al. **[9]**	He et al. **[10]**	He et al. **[11]**	Zhang et al. **[12]**
Is the case definition adequate (SELECTION)	-	*	*	*	-
Representativeness of the cases (SELECTION)	*	*	*	*	*
Selection of controls (SELECTION)	-	-	-	-	-
Definition of controls (SELECTION)	*	*	-	-	*
Comparability of cases and controls on the basis of the design or analysis (COMPARABILITY)	*	-	-	-	-
Ascertainment of exposure (EXPOSURE)	*	*	*	*	*
Same method of ascertainment for cases and controls (EXPOSURE)	*	*	*	*	*
Non-response rate (EXPOSURE)	-	-	-	-	-
Total	5	5	4	4	4

The research was then assessed qualitatively using the New Ottawa Scale. The New Ottawa Scale uses five aspects to evaluate research quality. These aspects are whether the case definition is adequate, representativeness of cases, selection of controls, definition of controls, Comparability of cases and controls on the basis of the design or analysis, Ascertainment of exposure, Same method of ascertainment for cases and controls, and non-response rate. The table presents a qualitative assessment of five studies on YAP expression using the New Ottawa Scale, evaluating aspects such as case definition, representativeness, control selection, comparability, and exposure ascertainment[8] received a total score of 5 points, excelling in representativeness, control definition, comparability, and exposure ascertainment, though it lacked an adequate case definition and selection of controls, also scored 5 points[9], with strengths in representativeness, control definition, and exposure ascertainment, but fell short in control selection and comparability, both scored 4 points[10,11]. These studies were strong in representativeness and exposure ascertainment but did not adequately define or select controls and lacked comparability. [12] also scored 4 points, with good performance in representativeness and exposure ascertainment but with limitations in case definition, control selection, and comparability. Overall, the assessment reveals that most studies were robust in ensuring representativeness and consistent exposure ascertainment but had varying weaknesses in control selection and comparability, affecting their overall quality ratings.

Table 2. Characteristics of included studies

Author, Year	Location	Design	Study Population	Total Sample	Age (yr)	Diagnostic Methods	Groups (n)	YAP Expression (%)
Liu et al., 2013 [8]	China	Case-control	Patients who underwent surgery at the Department of Gynecology of the Third Affiliated Hospital of Harbin Medical University between January 2003 December 2006	184	43.54±8.149	IHC	SCC (120)	Cytoplasm High: 30.83 Low: 69.17 Nuclear High: 0 Low: 0
							AC (42)	Cytoplasm High: 45.24 Low: 54.76 Nuclear High: 26.2 Low: 73.81

Xiao et al., 2014[9]	China	Case-control	Patients from the Pathology Department of the First Hospital affiliated with Shanxi Medical University during the period January 2006 to December 2011	180	NA	IHC	Chronic cervicitis (10) CIN 1 (49) CIN 2 (55) CIN 3 (34) SCC (32)	(0) 50 (1) 40 (2) 0 (3) 10 (0) 40.82 (1) 36.74 (2) 18.37 (3) 4.08 (0) 7.27 (1) 9.09 (2) 40 (3) 43.64 (0) 5.88 (1) 8.82 (2) 32.35 (3) 52.94 (0) 3.13 (1) 3.13 (2) 28.13 (3) 65.63
He et al., 2015 [10]	USA	Experimental, *in vivo*	Female athymic nude mice	79	6-week-old	IHC	Tumor (69) Normal (10)	Negative: 2.9 Weak: 5.8 Moderate: 13.04 Strong: 78.26 Negative: 60 Weak: 40 Moderate: 0 Strong: 0
He et al., 2019[11]	USA	Experimental, *in vivo*	KRT-rtTA and KRT14-	87	NA	IHC	Normal CIN I CIN II	Positivity: 0.36 Intensity (10^8): 0.286 Positivity: 0.41 Intensity (10^8): 0.286 Positivity: 1.10 Intensity (10^8): 6.43
Zhang et al., 2020[12]	China	Case-control	Patients who underwent surgically resected or biopsied from the First Affiliated Hospital of Bengbu Medical College from January 1, 2013, to December 31, 2014	151	27 – 70	IHC	CIN III	Positivity: 1.45 Intensity (10^8): 1.214

Characteristic results in five studies evaluating Yes-Associated Protein (YAP) expression in terms of location, study design, study population, total sample, age, diagnostic methods, study group, and YAP expression. The table summarizes five studies evaluating Yes-associated protein (YAP) expression using immunohistochemistry (IHC) in different populations and experimental conditions. A case-control study in China involving 184 patients from the Department of Gynecology[8], Third Affiliated Hospital of Harbin Medical University. They found that in squamous

cell carcinoma (SCC), cytoplasmic YAP expression was high in 30.83% of cases and low in 69.17%, while in adenocarcinoma (AC), 45.24% showed high cytoplasmic YAP expression and 26.2% had high nuclear YAP expression. Performed a similar study with 180 patients from Shanxi Medical University and observed that YAP expression increased progressively from chronic cervicitis to CIN and SCC,[9] with the highest expression in SCC (65.63%). Examined 79 female athymic nude mice and reported strong YAP expression in 78.26% of tumors compared to negligible expression in normal tissues.[10] In a follow-up experimental study.[11] used KRT-rtTA and KRT14-YAPS127A transgenic mice and found that YAP positivity and intensity increased with the severity of cervical intraepithelial neoplasia (CIN I to CIN III). Lastly,[12] investigated YAP expression in 151 patients at the First Affiliated Hospital of Bengbu Medical College, noting the highest expression (+++ 36.96%) in SCC, while normal tissues showed predominantly low expression levels. Overall, these studies collectively highlight the increasing YAP expression with disease progression, particularly in malignancies, underscoring its potential as a biomarker for disease severity and progression.

DISCUSSION

Cancer encompasses a collection of illnesses characterized by the unregulated proliferation and dissemination of irregular cells. The origins of cancer are varied, stemming from both internal and external factors, and their complexity means that our understanding remains partial. These causal elements can trigger the commencement of the cancer-forming process within the human body, potentially leading to fatality[13]. Cervical cancer, the most prevalent malignancy affecting the female cervix, emerges due to an infection by the Human Papilloma Virus (HPV)[2]. This form of cancer poses a significant global health challenge, ranking as the fourth leading cancer among women. In 2018, approximately 569,000 new cases were reported worldwide, contributing to around 311,000 cervical cancer-related deaths[14]. Various methods exist for managing cervical cancer, including primary, supplementary, and secondary treatment approaches[15].

Out of all these treatments, each one comes with its own set of side effects[15]. In recent times, numerous researchers have explored alternative methods to restrain the excessive growth of cancer cells and enhance the natural process of cancer cell death by utilizing the Hippo Signaling Pathway. The human hippo pathway comprises several fundamental routes, including Mst1-2, Sav1/WW45, Lats 1-2, MOBKL 1A-B, YAP, TAZ, and TEAD1-4. Within this crucial aspect, YAP and TAZ hold a significant role as transcriptional co-activators in contrast to the conventional hippo signaling. YAP and TAZ enter the nucleus of the cell and attach to TEAD, thereby prompting the activation of genes that promote growth. This mechanism also supports the regeneration of organs after they've been injured. However, irregular activation of YAP and TAZ, either due to disturbances in the Hippo pathway or an excessive presence of YAP, TAZ, and TEAD, can contribute to the development of cancer[6,7].

YAP overexpression was observed in cervical cancer across all five studies. This increased expression found in a wide range of human cancers indicates the potential of YAP to act as an oncogene. Similarly, the levels of YAP expression in Laryngeal Squamous Cell Carcinoma indicate that YAP overexpression serves as an independent prognostic biomarker functioning as an oncogene[16]. YAP can be classified as an oncogene due to its role in enhancing the regulation of cell replication, DNA synthesis, and repair. It also controls cyclin levels to facilitate entry into the "S" phase of the cell cycle and promotes completion of mitosis by triggering proto-oncogenic transcription factors, ultimately contributing to the manifestation of cancer cells[8,17].

Overexpression of YAP can lead to changes in cells that shift them from an epithelial to a mesenchymal state, a transformation commonly linked to the invasive and metastatic behavior of cancer cells. This shift, known as epithelial-mesenchymal transition, imparts aggressive traits like invasion, resistance to cell death, and reduced responsiveness to chemotherapy in advanced stages of disease. This process initiates when cell growth reaches a certain density. At this point, the Hippo pathway becomes active, prompting the expression of the Lats1/2 gene and its subsequent phosphorylation through a cascade of kinase reactions. YAP role involves diminishing the binding interaction of proteins within the nucleus, thereby impeding their function. Suppression of YAP/TAZ transcriptional function induces a state of cellular dormancy in the G1/S and G2/M phases, effectively stalling cell proliferation. Even when the Hippo pathway is deactivated, YAP/TAZ

continues its transcriptional activities without repression. Once YAP/TAZ enters the nucleus and binds to TEAD, it triggers cellular mitosis and proliferation, consequently promoting the transition from epithelial to mesenchymal state. Within cancer cells, YAP and TAZ are crucial in driving the epithelial-mesenchymal transition (EMT). This transition initiates processes such as self-renewal in cancer stem cells via TAZ activation and promotes EMT through interaction with AP-1 FOS components via YAP. During EMT, epithelial cells lose their apical-basal polarity, detach from the basement membrane, and weaken intercellular connections. In cancer cells, EMT is closely associated with characteristics such as cancer stem cell traits, resistance to apoptosis, and decreased susceptibility to drugs[8,17–21].

The process of epithelial-mesenchymal transition, in which YAP plays a role, plays a part in the development of cancer and the formation of tumors[20]. Another way in which YAP is involved in the development of tumors is through the varying levels of its expression within a tumor. This happens because tumor cells that express YAP at different intensities will engage in competition with neighboring cells. As these cells interact, the ones with higher YAP expression will experience boosted growth and stimulate the activation of genes associated with cancer[22].

YAP expression is found in two distinct cellular locations: the cytoplasm and the nucleus. In the normal and CIN I groups, YAP expression is primarily observed in small amounts within the cell cytoplasm. This indicates that when YAP is located in the cytoplasm, its role as a cancer initiator is diminished, although it might still contribute to the onset of cervical cancer and play a critical role in the differentiation of mature airway epithelial progenitors. Conversely, in the CIN II, III, SCC, AC, Early, and Advanced Cancer groups, YAP expression is predominantly concentrated within the cell nucleus. This suggests that YAP presence in the nucleus influences tumor development and cellular growth, suppresses differentiation, and hampers programmed cell death. Hence, YAP function within the nucleus is pivotal in the progression of CIN (cervical intraepithelial neoplasia) towards cancer. These differing subcellular distributions of YAP expression across tissue samples correspond to variations in its functionality, depending on whether YAP is located in the cytoplasm or the nucleus. In the cytoplasm, the presence of LATS 1/2 prompts phosphorylation of YAP, leading to its interaction with 14-3-3 proteins and subsequent ubiquitination, resulting in YAP degradation. However, when YAP is transported into the nucleus, it interacts with TEAD1-4 and releases VGLL4 to activate gene transcription, fostering tissue growth and restraining programmed cell death[9,23,24].

Past research has indicated that maintaining a proper balance of YAP in both the nucleus and cytoplasm is essential for controlling the way lungs develop in mice. If YAP is situated in the cytoplasm, its ability to encourage the advancement of tumors diminishes. On the other hand, when YAP is present in the nucleus, it influences the activation of different genes that play a role in the growth and multiplication of cells. This phenomenon is linked to changes and reduced activity of the main elements of the Hippo pathway[25].

The excessive activity of YAP has a significant impact on the health of patients. Individuals who exhibited high levels of YAP, TAZ, and β-catenin had unfavorable prospects, as indicated by lower chances of survival and shorter survival times compared to those with lower expressions. Another investigation suggested that the excessive presence and distribution of YAP in Ovarian Serous Cystadenocarcinoma were connected to unfavorable survival rates. Additionally, a separate study[11] found that patients with notable YAP1 amplification/ deletion or mutations in tumor suppressor genes experienced worse outcomes compared to those without any genetic alterations[11,12,26].

YAP plays a crucial part in determining the functions of cells in different subtypes of cervical carcinoma. These functions encompass cell proliferation, apoptosis, cell survival, and cell migration. Changes in how YAP is expressed and where it's located within cells can hold varying clinical significance depending on the type of tumor. As a result, it's reasonable to consider YAP role as a possible indicator of prognosis for cervical cancer. This is because higher levels of YAP expression in human cervical cancer tissues correlate with the advancement of cervical cancer. Furthermore, there's potential to target YAP for therapeutic purposes in cervical cancer treatment, given that cancer cells frequently resist cell death by inhibiting pathways related to apoptosis[10,17].

Cervical cancer develops due to an infection with high-risk forms of Human Papilloma Virus (HPV), specifically HPV 16 and 18. These types

of HPV are commonly found in healthy women and can sometimes regress on their own. While high-risk HPV infection is a crucial factor in the development of cervical cancer, it alone isn't sufficient to initiate and propel the progression of this cancer. The irregular functioning of the Hippo pathway might play a role in starting and advancing HPV-triggered cervical cancer. In cervical cancer cells, HPV E6/E7 can hinder the degradation of YAP through mechanisms involving the suppression of negative YAP regulators like MST1, PTPN14, or SOCS6. Furthermore, HPV E6 encourages the buildup of YAP, TAZ, and TEAD proteins and the genes they regulate. As a result, elevated YAP levels could lead to persistent HPV infection by increasing the expression of HPV membrane receptors and dampening the host's innate immune response[10,27–29].

Besides YAP, the TAZ protein also plays a role in cancer development. TAZ is a protein that is easily degraded and becomes unstable in densely packed cell environments. This relationship between TAZ expression, stability, and cancer development is significant in carcinogenesis and has been observed in various types of human cancer. Although previous research has shown elevated TAZ levels in cervical cancer, the precise mechanisms of TAZ expression and function in cervical cancer cells are not yet fully understood. Immunofluorescence studies have identified TAZ expression in a specific group of cells in both normal cervical tissue and squamous cell carcinoma (SCC)[30].

Examination using immunofluorescence revealed that TAZ was notably more prevalent in the nucleus and cytosol of normal tissues compared to both SCC tissues and metastatic SCC tissues. This distinct pattern of TAZ expression was particularly noticeable in the basal layer cells of normal cervical tissue but was absent in SCC tissues. These locations of TAZ expression indicate a widespread process of controlled breakdown, while the movement of TAZ into the nucleus could suggest that TAZ is triggering cancer-causing genetic programs. This implies that the Hippo pathway mainly influences TAZ by regulating its movement between the cell's fluid and the nucleus. The presence of TAZ in the cytoplasm might play a role in initiating or advancing abnormal tissue growth. This investigation established a connection between TAZ expression in both the nucleus and cytosol and SCC, partly because TAZ was observed to relocate to the cytosol within SCC tissues[30].

Based on the qualitative assessment of studies on Yes-associated protein (YAP) expression in cervical pre-cancerous lesions and cervical cancer, it is evident that YAP plays a critical role in the progression of cervical cancer. The systematic review identified five studies that were qualitatively evaluated using the New Ottawa Scale, focusing on aspects like case definition, representativeness, control selection, comparability, and exposure ascertainment. The studies showed variations in quality, scoring the highest (5 points each), indicating robust methodologies in control definition, exposure ascertainment, and representativeness[8,9], albeit with minor shortcomings in case definition and control selection. In contrast, scored 4 points each,[10-12] demonstrating strengths in representativeness and exposure ascertainment but lacking in control definition and selection. Across all studies, the consistent finding is the elevated expression of YAP in both the cytoplasm and nucleus of cervical cancer cells compared to normal tissues. This heightened expression correlates with the severity and advancement of the disease, highlighting YAP's potential as both a biomarker for cervical cancer and a therapeutic target. These findings substantiate the hypothesis that YAP expression plays a pivotal role in cervical cancer development and progression, influenced by its localization within cells and its interactions with components of the Hippo signaling pathway.

Further meta-analysis studies concerning YAP expression in cervical cancer is recommended to provide a unified perspective by integrating quantitative data and outcomes from randomized controlled trials (RCTs), thereby aiding in the evaluation of YAP's viability as both a therapeutic target and biomarker.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Systematic Review

Effectiveness of the Telemedicine Approach on Maternal Health Practices among Pregnant Women in Rural Areas

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Abstract

Objectives: To systematically evaluate the current evidence on the effectiveness of the telemedicine approach on maternal practices in rural communities. The author hopes that this study offers a breakthrough to draw a solid conclusion regarding the feasibility of implementing telemedicine to improve maternal health in rural areas of Indonesia.

Methods: A systematic literature search was performed using international databases, such as Cochrane, PubMed, EBSCOhost, Science Direct, Scopus, and Google Scholar, published from 2012 to August 31, 2022. Risk of bias assessment was conducted using the Cochrane Risk of Bias tools 2.0 for randomized controlled trials and converted to the AHRQ standards.

Results: This study included five randomized controlled trials from different countries, namely India, Ethiopia, and Kenya. Telehealth interventions, delivered using mobile applications, phone calls, or short text messaging, improved the number of ANC visits, safe childbirth in hospitals or by skilled staff, exclusive breastfeeding, and immunization compliance, with a significant difference compared to the control group that received no intervention ($p<0.05$). Nevertheless, considering the already widely used mobile phone technologies in rural settings, it is now clear that the telehealth approach should be scaled up and implemented in clinical settings.

Conclusion: Telehealth-based intervention is a promising approach to promote better maternal health practices among pregnant mothers in rural and low-resources settings. This approach has been proved to successfully made a significant difference in terms of antenatal care visits and safe childbirth practice.

Keywords: Maternal health practices, pregnant women, rural areas, systematic review, telemedicine.

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INTRODUCTION

In Indonesia, maternal mortality in rural areas has been a significant issue for decades. According to data from the Riset Kesehatan Dasar (Riskesdas) by the Ministry of Health, Republic of Indonesia, in 2018, there remains a substantial disparity in antenatal care coverage between provinces, with the lowest in Papua (66.8%) and the highest in Central Java (99.0%).[1] In certain rural areas of Indonesia, including West Papua, Papua, and East Nusa Tenggara, maternal mortality rates have been alarmingly high, with figures reaching 565, 343, and 316 per 100,000 live births, respectively, according to data from the Long Form Sensus Penduduk 2020 by Badan Pusat Statistik. These rates are significantly higher than the national average of 189 per 100,000 live births.[2] The most critical factors contributing to maternal mortality are maternal education and rural residence, with odds ratios of 5.74 and 4.65, respectively.[3] It occurs in women undergoing regular antenatal care at midwives without a risk factor analysis recorded.[4] Therefore, novel solutions are urgently required, especially in rural areas.

The significant cognitive, structural, and financial barriers have made access to healthcare facilities in rural areas nearly impossible. The failure of the educational function among

healthcare workers has a massive impact on maternal and infant mortality rates. This is due to the fact that pregnant mothers need much more careful treatment and proper education by the healthcare workers. However, in rural areas, only half of the pregnant mothers receive at least four antenatal care (ANC) visits. Moreover, the rate of safe delivery in hospitals by skilled nurses and midwives remains relatively low. This condition leads to various complications during and after pregnancy and childbirth, resulting in a high mortality rate.[5,6]

With advancements in health technology, especially telemedicine, it is now possible to connect patients with professional healthcare workers in a much more effective and efficient manner. According to the International Telecommunication Union, there were over seven billion mobile phone users worldwide in 2015, and over 90% of the population in low-to middle-income countries had access to mobile phone.[7] Through the telehealth approach, healthcare can be delivered using mobile applications, phone calls, or short text messaging. Recent studies conducted in India, Kenya, and Ethiopia have shown that telehealth approaches have significantly improved maternal health through routine education and reminders to maintain good health among pregnant women.[8,9] These countries have similar socioeconomic backgrounds to Indonesia; therefore, they may represent conditions similar to those in Indonesia.

However, most review studies conducted to date have not reported and analyzed outcomes in rural areas alone, with most studies combining the results in urban and rural communities. Through this systematic review, the author focused on the effectiveness of the telehealth approach on maternal practices in rural communities. The author hopes that this study offers a breakthrough in drawing a solid conclusion regarding the feasibility of implementing telehealth to improve maternal health in rural areas of Indonesia, especially in West Papua, Papua, and East Nusa Tenggara.

METHODS

The study was conducted in accordance with the Cochrane Handbook 6.2 and is reported based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline.[10]

A Literature search was performed in databases including Cochrane, PubMed, EBSCOhost, Science Direct, Scopus, and Google Scholar for studies that implemented a telehealth-based approach to maternal health education from 2012 to August 31, 2022, with the detailed keywords for each database, as shown in **Table 1**. Furthermore, an advance search strategy was used whenever appropriate to narrow the search process.

Table 1. Table of Keywords for Literature search

Database	Keywords
PubMed	(("telemedicine"[MeSH Terms] OR telemedicine[Text Word]) AND ("gravidity"[MeSH Terms] OR pregnant women[Text Word]) AND (("health"[MeSH Terms] OR health[Text Word]) AND ("knowledge"[MeSH Terms] OR knowledge[Text Word])) AND ("Rural Population "[Mesh])
Scopus	TITLE-ABS-KEY ((telemedicine OR telehealth OR ehealth OR e-health OR health OR m-health) AND (pregnancy OR pregnant or prenatal or antenatal or perinatal or maternal) AND (maternal health knowledge) AND (rural areas of rural communities more rural patients or rural population or remote))
Cochrane	(("telemedicine"[MeSH Terms] OR telemedicine[Text Word]) AND ("gravidity"[MeSH Terms] OR pregnant women[Text Word]) AND (("health"[MeSH Terms] OR health[Text Word]) AND ("knowledge"[MeSH Terms] OR knowledge[Text Word])) AND ("Rural Population "[Mesh])
EBSCOhost	(telemedicine OR telehealth OR ehealth OR e-health OR health OR m-health) AND (pregnancy OR pregnant or prenatal or antenatal or perinatal or maternal) AND (maternal health knowledge) AND (rural areas of rural communities more rural patients or rural population or remote)
ScienceDirect	(telemedicine OR telehealth OR ehealth OR e-health OR health OR m-health) AND (pregnancy OR pregnant or prenatal or antenatal or perinatal or maternal) AND (maternal health knowledge) AND (rural areas of rural communities more rural patients or rural population or remote)
Google Scholar	(telemedicine OR telehealth OR ehealth OR e-health OR health OR m-health) AND (pregnancy OR pregnant or prenatal or antenatal or perinatal or maternal) AND (maternal health knowledge) AND (rural areas of rural communities more rural patients or rural population or remote)

The inclusion criteria were as follows: type of study, randomized controlled trial; population, pregnant mothers who have access to mobile phones and reside in rural areas; intervention, maternal education through telehealth approaches; and outcomes, maternal knowledge and practices. The exclusion criteria were set as follows: unsuitable study design; incomplete result data; inability to retrieve full-text articles; no control group; and languages other than English.

In this systematic review, the author carefully reported the key findings and key information from each included study. The following data were extracted: author and time of publication; characteristics of the study, including study design and location; population of the study by number and mean age, intervention, program characteristics, and results, detailed in the indicators, pre- and post-intervention values, and significance levels (p-values).

The quality of each study was assessed using the Cochrane Risk of Bias 2.0 for randomized controlled trials. This tool consists of five domains: risk of bias due to the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcomes, and bias in selecting the reported result. Subsequently, the overall quality of the study was determined based on the Agency for Healthcare Research and Quality (AHRQ) standards.

RESULTS

A flowchart of the literature search is shown in **Figure 1**. The initial search returned 289 records from all databases. 244 records were further screened by titles and abstracts, and 101 articles were excluded. Unrelated articles, comments, reviews, letters, and duplicates were excluded. Subsequently, 36 articles were assessed by accessing their full text. Nineteen studies were excluded because of qualitative outcomes, eight studies were irretrievable full texts, and four studies were in languages other than English or Indonesian. Finally, five studies were included in the analysis. A summary of the bias assessment is provided in **Appendix 1**. In summary, we found that all studies included in this review were of good quality in terms of the AHRQ standards. Therefore, all the studies included in this review had a low risk of bias.

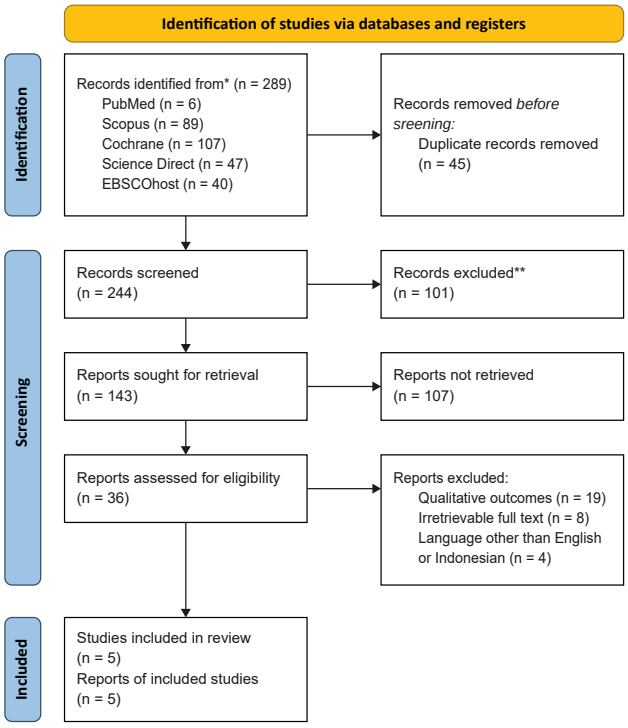

Figure 1. Literature search strategy diagram

All five studies included were randomized controlled trials that were conducted in rural areas among low-to-middle income countries, namely India, Ethiopia, and Kenya. These studies were conducted over multiple years from 2014 to 2020. Among the included studies, the participants were pregnant mothers without gestational age limitations residing in rural areas. Patients included in the studies had access to mobile phones with adequate internet connection. The intervention includes a telehealth-based approach to maternal education programs, including ANC, nutrition, and immunization for infants, and a safe delivery process. In contrast, the control group received only routine ANC sessions, without any telehealth intervention. The outcomes measured were the number of ANC visits during pregnancy, place of delivery, breastfeeding practice, and immunization status related to pregnancy. In **Table 2**, the characteristics of the included studies are presented and in **Table 3** the study results are showed.

Table 2. Study characteristics

Author; year	Study design	Location	Population	Number of participants (Mean age ± SD)	Intervention	Control	Duration of intervention
Bangal et al[11], 2017	RCT	Ahmednagar, India	Pregnant women voluntarily coming for antenatal visit at Rural Medical College, Loni, Ahmednagar	Intervention: 200; age not available Control: 200; age not available	Healthcare workers perform regular mobile phone calls to mothers to remind for next visit schedule, in addition to SMS text messaging about important education of ANC and its aspects.	Routine ANC care without mobile phone calls and SMS	1 year
Murthy et al[12], 2020	Pseudo RCT	Mumbai, India	Pregnant women from two wards (F North and M East).	Intervention: 1,113; 25 (3.9) y Control: 402; 24 (4.1) y	A mobile application program named mMITRA deliver one hundred and forty-five audio messages.	No intervention	1 year
Atnafu et al[13], 2017	RCT	Abeshge, Ethiopia	Pregnant mothers from three woredas, namely Ezha, Abeshge, and Sodo	Intervention: 1,073; age not available Control: 1,080; age not available	SMS text messaging–based mobile phone reminder intervention about ANC and delivery services.	No intervention	13 months
Unger et al[14], 2018	RCT	Nairobi, Kenya	Pregnant women at the Mathare North Health Centre (MCH).	Intervention: 100; 23 (20 -26) y Control: 99; 24 (21 -26) y	SMS text messaging automatedly sent to participants including topic such as ANC, pregnancy complications, family planning, infant health, infant immunization, and visit reminders.	Routine ANC without SMS text messaging	24 weeks
Fedha et al[15], 2014	RCT	Njoro, Kenya	Pregnant women with gestation age between 12-36 weeks	Intervention: 191; age not available Control: 206; age not available	Mobile phone reminders and updates on pregnancy condition every fortnightly, including ANC and pregnancy advices.	Routine care with no mobile reminders or supports	Until 6 weeks post-delivery

*Significant results. Abbreviations: ANC: antenatal care.

Table 3. Key study outcomes

Author; year of publication	Study outcomes			
	Indicators	Intervention	Control	Significance *(P-value)*
Bangal et al[11], 2017	ANC visits 6 or more (%)	24	24	<0.0001
	Delivery at hospital (%)	91.5	91.5	N/A
	Tetanus toxoid immunization (%)	97.29	97.29	<0.0002
Murthy et al[12], 2020	ANC visits 3 or more (Intervention/control)	1.508 (0.797–2.853)		0.207
	Delivered in hospital (Intervention/control)	2.543 (1.488–4.348)		0.0001*
	Delivery by skilled birth attendant at home deliveries (Intervention/control)	0.457 (0.229–0.913)		0.027*
	Mother fed colostrum to the baby	1.269 (0.898–1.794)		0.177
Atnafu et al[13], 2017	ANC visits 4 or more (%)	Baseline: 15.80 Post intervention: 31.50	Baseline: 24.48 Post intervention: 23.27	0.0001*
	Delivered in hospital (%)	Baseline: 49.30 Post intervention: 64.18	Baseline: 27.20 Post intervention: 41.54	0.0001*
Unger et al[14], 2018	Exclusive breastfeeding practice	0.62 (0.51-0.72)	0.41 (0.31-0.51)	0.005 *
	Postpartum contraceptive use	0.83 (0.75-0.90)	0.77 (0.69-0.85)	0.33
Fedha et al[15], 2014	ANC visits 4 or more (%)	96.4	82.4	0.002*
	Delivery in hospital (%)	88.0	72.8	<0.001*
	Number of participants taking iron supplements (%)	91.6	87.4	0.170
	Tetanus toxoid immunization (%)	100	99.7	0.534

*Significant results. Abbreviations: ANC: antenatal care.

Antenatal Care Visits

The impact of the telehealth approach in terms of ANC visits was consistently reported to be superior to the control group in four studies. Study by Bangal et al reported that the number of ANC visits of 6 or more in the intervention group was 24%, while in the control group was 7% with significant p-values ($p<0.0001$).[11] Study by Atnafu et al and Fedha et al showed that the ANC visits 4 or more in the intervention group significantly improved ($p=0.0001$ and $p=0.002$, respectively).[13,15] However, study by Murthy et al reported that the ANC visits was not significantly different between intervention and control group ($p=0.207$).[12]

Safe Delivery

The location of delivery is one of the most important factors for safe delivery. The telehealth approach was proven to have a beneficial outcome to ensure that delivery was done in a hospital by a skilled birth attendant in a sterile environment. Three studies by Murthy et al., Atnafu et al., and Fedha et al. reported that mothers given telehealth interventions were most likely to deliver their babies in the hospital ($p<0.0001$).[12,13,15] This finding was consistent in each study and showed superiority of telehealth compared to the control group. One study by Bangal et al also reported that overall percentage of women delivered in hospitals were higher in the telehealth intervention group than control group, however the significance value was not showed in the study.[11]

Breastfeeding Practice, Postpartum Contraception, and Immunization Compliance

Other outcomes reported by the included studies were the impact of the telehealth approach on breastfeeding practices, postpartum contraception, and immunization compliance. Studies reported that mothers who received telehealth intervention were most likely compliant with exclusive breastfeeding of their baby compared to the control group, which was not given any intervention.[12,14] A significant difference ($p=0.005$), while insignificant results.

Postpartum contraception with no significant differences were found. In the study, both 1-way and 2-way SMS approaches increased early uptake of contraception by 16 weeks postpartum, though this was not statistically significant when correcting for multiple comparisons.[14]

Finally, immunization compliance was assessed and reported the compliance to tetanus toxoid immunization found significant results ($p<0.0002$), while study no significant differences ($p=0.534$).[11,15]

DISCUSSION

Technology development in rural areas has increased greatly since the start of the modernization era.[16] In fact, the International Telecommunication Union launched the results from their survey that there were already over 7 billion people who had access to mobile phones in 2015, with its benefits in rural communities reaching 90% of the population.[7] Telemedicine, which combined healthcare with technologies, has helped human health in various ways, from prevention and education to home monitoring of specific conditions. Moreover, its role in assisting pregnant women from routine monitoring and check up to various maternal health education are also crucial.[16]

In this study, the telehealth approach focuses on several topics related to maternal health practices. These approaches consist of reminders and educational content that cover several subtopics such as pregnancy nutritional need, vitamin and mineral supplementation, ANC reminders, birth preparedness, mental health during pregnancy, and exclusive breastfeeding practices. Moreover, other studies also included education about basic immunization needs in pregnancy to prevent dangerous infections during pregnancy. Telehealth approach was delivered by several means, namely phone calls, mobile application, and short message services (SMS) according to the available technology and the competence of the population in each study.[14]

According to the World Health Organization recommendation, there are several practices that is required for pregnant mothers, such as nutritional needs, maternal and fetal assessment, preventive measures, intervention for physiological symptoms, and antenatal care visits.[17] The included studies measured the number of ANC visits during the whole pregnancy period, safe delivery in hospital or by skilled professionals, exclusive breastfeeding, and immunization compliance.[18]

WHO guidelines suggest that antenatal care visits should ideally be performed in 13 visits, specifically once a month for the first 7 months, twice a month for the next month, and once a week for the last gestational month until delivery. Meanwhile, the minimum requirement recommended by the WHO is four contacts or visits to reduce the risk of perinatal mortality and promote a positive mother's pregnancy experience.[19] In our included studies, ANC visits of more than four were reported.[11,13,15] They reported that telehealth interventions, specifically through routine reminders of the next ANC visits, could significantly improve the practice of ANC visits among pregnant mothers

The next health practice measured was safe delivery. Safe delivery requires several factors, such as the presentation of professional staff, continuous monitoring of the mother and fetal condition, administration of antibiotic therapy, and other interventions when appropriate.[20] WHO guideline suggest that delivery should only be performed under the supervision of professional healthcare workers, including midwives. The studies included in this review reported that after telehealth intervention in terms of education on safe childbirth, the number of pregnant mothers who delivered their babies in the hospital increased in contrast to the control group. There is significant difference of the number of deliveries in hospital ($p<0.0001$) and deliveries by skilled staffs ($p=0.027$).[12]

This systematic review has several strengths and limitations. First, it provides evidence regarding the effectiveness of a telehealth-based approach to maternal health practices among pregnant mothers in rural areas. Second, the author compared data from the included studies to provide insight into the importance of telehealth-based approaches. However, the author also identified limitations of the study, the included studies showed high heterogeneity in the included subjects of various gestational age.

CONCLUSION

Telehealth-based intervention is a promising approach to promote better maternal health practices among pregnant mothers in rural and low-resources settings. This approach has been proved to successfully made a significant difference in terms of antenatal care visits and safe childbirth practice.

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