Editorial

Integrating Herbal Remedies in Indonesian Obstetric and Gynecologic Care: Bridging Tradition with Modern Medicines

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Indonesia is one of the richest places in the world for medicinal plants. It has over 30,000 plant species and a wide range of marine resources. This natural abundance positions Indonesia as a prominent global exporter of herbal medicinal goods. Notwithstanding its abundant natural resources, merely a minor percentage of Indonesia's 19,871 recognized medicinal plants are utilized for industrial applications—approximately 200 species are employed as raw materials for herbal goods. The nation's extensive biodiversity remains largely unexploited, posing both a challenge and an opportunity for the herbal medicine sector. Nonetheless, the utilization of this vast repository remains inadequate.[1,2] Of the roughly 9,600 plant and animal species identified for their therapeutic properties, only a limited number have progressed to become widely utilized or commercially viable herbal medicines. This disparity underscores the imperative to utilize and protect this potential. To maintain Indonesia's global competitiveness, research and innovation in herbal medicine must transcend academic requirements and focus on tangible product and industry advancement. Despite extensive study by educational and research organizations, insufficient downstream prospects have resulted in many results remaining uncommercialized, so failing to convert research into important health products. [3,4]

In 2019, Indonesia ranked 19th among exporting nations, holding just 0.61% of the world herbal medicine market. However, the sector showed robust growth with a 14.08% export increase from January to September 2020, amounting to USD 9.64 million. Major buyers include India, Singapore, Japan, Malaysia, and Vietnam. Herbal medicine remains a key element of healthcare. Its popularity spans both developing and developed countries. [1,2]

The use of herbal remedies is deeply rooted and widespread in Indonesian obstetric and gynaecological care, particularly in pregnancy, postpartum recovery, lactation, and menstrual disorders. While cultural acceptance is high, scientific evidence regarding their safety and efficacy is growing but remains incomplete. Common herbal uses and indications include pregnancy such as ginger (*Zingiber officinale*), turmeric (*Curcuma longa*), and tamarind (*Tamarindus indica*) are frequently used to relieve nausea, fatigue, and back pain during pregnancy. These herbs are valued for their perceived "natural" origin, affordability, and cultural comfort. For lactation, herbs such as *Moringa oleifera* and katuk (*Sauropus androgynus*) are widely used as galactagogues to enhance breast milk production. Multiple studies have demonstrated the positive effects of these practices on milk volume and infant nutrition. Integrating them into both traditional and modern health initiatives, postpartum care involves the consumption of herbal mixtures by postpartum women. These mixtures are aimed at accelerating recovery, reducing uterine cramping, control the bleeding, and restoring strength. Popular plants include turmeric, tamarind, katuk, binahong, and turi leaf (Sesbania grandiflora). Ginger-based jamu is believed to assist recovery and uterine health. Menstrual disorders, turmeric is a commonly cited remedy for dysmenorrhea (menstrual pain), with studies supporting its effectiveness among Indonesian adolescents. Women's General Health. Other plants often cited include piper betle, kaempferia galanga, and leaves from vegetables grown locally (e.g., binahong), targeting a variety of women's health issues such as leukorrhea and pre-menstrual symptoms. [5,6]

Herbal medicine is deeply integrated into Indonesian obstetric and gynaecological practice, with distinct regional preferences and a variety of botanicals used to address pregnancy discomfort, postpartum care, lactation, and menstrual symptoms. While many herbs are culturally ingrained and widely accepted, scientific evaluation of their safety and efficacy remains partial, highlighting the need for ongoing collaboration between traditional and medical practitioners for safe reasons. [5,6]

Research imperatives and future directions to firmly establish herbal medicine within modern medical regimes, research quality must dramatically improve across primary areas. Herbal medicine quality and standardisation, ensuring quality from source material is needed to authenticate and assure reproducibility. Preclinical pharmacological assessments, standardized products should undergo thorough safety and efficacy evaluation in carefully controlled laboratory and animal studies. [5,6]

Comprehensive collaboration between traditional and modern medicine in the use of herbal materials as modern medicines requires an integrated approach involving scientific research, standardisation and product development. This includes research on collaboration steps, scientific research, including preclinical trials, active compound identification, and pharmacological research. Raw material and product standardisation to stablish quality standards for herbal ingredients, including identification of species, plant parts used, drying methods, and active compound concentrations. Interdisciplinary collaboration between researchers, herbal practitioners, and the pharmaceutical industry. Building close collaboration between researchers from various disciplines, traditional medicine practitioners, and the pharmaceutical industry and providing training and education to healthcare workers on the safe and effective use of herbal medicines and increasing understanding and recognition of traditional medicine as part of a comprehensive healthcare system with implementing clear and consistent regulations regarding the production, distribution, and use of herbal medicines. [5,7]

Despite widespread use, questions over scientific validation, safety, and dose persist, underscoring the necessity for integration with evidence-based contemporary obstetric care. Indonesia presents an exceptional variety of indigenous herbal and plant-based options for women's health, rooted in profound regional traditions. These resources are significant in obstetric and gynecological treatment, particularly in rural and culturally conservative settings. Integrating indigenous knowledge with contemporary therapeutic practices—ensuring efficacy and safety—could significantly improve women's health. Indonesia provides an exceptional variety of indigenous herbal and plant-based options for women's health, rooted in profound regional traditions.

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Research Article

Characteristics and Treatment in Patients with Vaginismus in Surabaya, East Java, Indonesia

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Abstract

Background: Vaginismus is still an under-researched case of women's health despite its universal prevalence.

Aim: This study aims to explore the characteristics of vaginismus in East Java, Indonesia.

Methods: The subjects in this study were all new female patients with Vaginismus found in a single hospital, Surabaya, East Java, Indonesia, in 2022. The data used in this study are secondary data obtained from the medical records. Descriptive data are presented as numbers and percentages for categorical data.

Results: Vaginismus was found in a single hospital - East Java, Indonesia. Based on medical record data, throughout 2022, there will be 60 patients with a diagnosis of Genito-Pelvic Pain Penetration Disorder (GPPPD). The assessment of patient characteristics showed that almost all patients were of reproductive age. Most of the respondents have been married for more than 1 year. Management is carried out independently and collaboratively. A total of 60 patients underwent anamnesis and physical examination. Complaints experienced by patients are the failure to penetrate. Treatment was done using Botox injections, dilatation, hymenectomy, and consultation with a psychiatrist and an andrologist.

Conclusion: Management in cases of Vaginismus requires cross-professional collaboration, such as psychiatrists and andrologists. The treatment given also tends to be complex.

Keywords: pelvic pain penetration, hospital, women's health.

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INTRODUCTION

Vaginismus is an involuntary spasm of the vaginal muscles that interferes with sexual intercourse. Study on the epidemiology of these cases is rarely done. This is due to the lack of research interest in terms of diagnostic, etiological, or treatment results. These cases tend to be difficult to diagnose or treat, resulting in the unavailability of definitive epidemiological data regarding the prevalence of vaginismus in the population. Investigators will require stressful gynecological examinations that sufferers may often avoid. Consequently, there are various estimates of the prevalence of this problem. Not everyone will report this problem, and women with this disease are vulnerable to being marginalized.[1] A systematic review reported that the incidence of vaginismus in the general population of women was reported to be 0.4% to 8%.[2]

Women who experience Vaginismus can experience various problems, such as infertility. The risks do not stop until the woman can get pregnant. Pregnant women with vaginismus are at risk of not being followed up during their pregnancy because of feelings of shame and a lack of understanding by medical staff. These cases may affect a woman's perception of her femininity and her potential for motherhood.[3]

Infertility impacts the mental health, quality of life, and sexual connection of a couple.[4]

The variables of fear of sex, positive cognition and negative self-image, sexual intimacy, quality of sexual life, and education were the final predictors of vaginismus diagnosis score.[5] One of the predictors of successful treatment for vaginismus is the attribution of the problem to psychological causes rather than physical. In order to fully understand vaginismus, it must be explored at intrapersonal, interpersonal, and cultural levels, and of all of these, the interpersonal level continues to be under-researched.[6]

Vaginismus is predominantly unknown among clinicians and women. It is a poorly understood and underdiagnosed condition, for which many women do not gain support. To understand cases and detect them early, clinicians and researchers need to understand the characteristics of the patient and the therapies that have been carried out before. This study aims to explore the characteristics of vaginismus patients in East Java, Indonesia.

METHODS

This is a descriptive observational study with a cross-sectional approach. The subjects in this study were all new female patients with Vaginismus who were found in a single hospital, East Java, Indonesia, in 2022. The data used in this study are secondary data obtained from the medical records. Descriptive data are presented as numbers and percentages for categorical data.

RESULTS

Vaginismus was found in a single hospital - East Java, Indonesia. Based on medical record data, throughout 2022, there will be 60 patients with a diagnosis of vaginismus. The results of the assessment of patient characteristics showed that almost all patients were of reproductive age. A total of 56 respondents aged 20-35 years (93%) and 4 respondents aged more than 35 years (7%). Most of the respondents have been married for more than 1 year. Married less than 1 year, there were 6 people (10%), 1-5 years, 49 people (82%), and more than 5 years as many as 5 people (8%). Based on the table, the most frequently reported symptom was pain and fear during attempted vaginal intercourse, experienced by 56 respondents (93%). A smaller proportion of respondents reported a burning sensation in the vulvar area (3 respondents, 5%), while 1 respondent (2%) experienced a tightening sensation in the lower abdomen, perineum, buttocks, and upper thighs. These findings indicate that the primary complaints among respondents are pain and muscle tension in the genital area, which may suggest conditions such as vaginismus or dyspareunia.

Table 1. Characteristics of patients

Variable	Category	Total (Percentage)
Age	20-35 years	56 (93%)
	>35	4 (7%)
Duration of marriage	< 1 year	6 (10%),
	1-5 years	49 (82%)
	> 5 years	5 (8%).
Symptoms	Tightening sensation in the lower abdomen, perineum, buttocks, and upper thighs	1 (2%)
	Pain and fear at attempted vaginal intercourse	56 (93%)
	Burning in the vulva area	3 (5%)

Management is carried out independently and collaboratively. A total of 60 patients underwent anamnesis and physical examination. Complaints experienced by patients are the failure to penetrate. The doctor examines by trying to insert 1 index finger. 3 patients failed the examination due to severe pain. Of the 3 patients, 2 were given Botox injections and 1 was referred to a psychiatrist because they did not want Botox and admitted that they had psychological trauma. Both patients who received Botox injections managed to continue with independent dilatation, and 1 patient managed to get pregnant. Of the other 57 patients, all underwent gynecological evaluation and successful finger insertion. However, 2 patients had problems with the hymen. The condition of the patient's hymen is one small hole, and the hymen is thick and stiff. The patient was then operated on for hymenectomy. Of the 55 patients whose finger insertion was successful, patients were trained to perform independent dilation with silicone dilators of sizes 1 to 5. Among the remaining 55 patients, there were 5 patients who had difficulty

dilating independently, so Botox injections were performed. A total of 7 patients who underwent surgery or Botox were able to continue with independent dilatation. This success is aided by dilators. Of the 60 patients, there was 1 patient who was consulted by a psychiatrist who was still practicing dilators, and 5 people with independent dilation (without Botox and without surgery) who were still practicing with dilators. One patient practiced self-dilatation; her husband had erectile dysfunction and was therefore referred to an andrologist.

DISCUSSION

Case analysis shows that each patient has their own characteristics, so they require treatment according to the problem. Management in cases of Vaginismus requires cross-professional collaboration, such as psychiatrists and andrologists. The treatment given also tends to be complex. Treatment has been carried out using vaginal dilators, psychotherapy, and psychiatric care. Gentle care and sensitive listening should be integral components in multidisciplinary teamwork to identify women with vaginismus and offer partners better quality care.[7] The use of a multidimensional approach in this study led to the acceleration of the diagnosis and treatment of vaginismus.[8] One of the predictors of successful treatment for vaginismus is the attribution of the problem to psychological rather than physical causes. [6]. A multimodal program that treated the physical and psychological aspects of vaginismus enabled women to achieve pain-free intercourse, as noted by patient communications and serial female sexual function studies.[9]

There are patients undergoing hymenectomy. This causes difficulties when penetrating. Another study examined the use of hymenectomy in patients undergoing cognitive behavioral treatment alone. One of the most common anatomical causes is hymen abnormalities. Treatment of vaginismus is facilitated by removing the physical barrier through hymenotomy or hymenectomy when there is a septate hymen with a half-moon shape and a high edge or an inflexible hymen.[10] In addition to the treatment using hymenectomy, the other treatment is Botox injection. This is in accordance with other study, who conducted a meta-analysis study. Botox injection can be an option for vaginismus patients and is effective even though the number of RCT studies is still limited [11]. Chronic pelvic pain, vaginismus, and vulvar and vaginal dyspareunia have all been observed to improve after botulinum toxin injections. No permanent adverse consequences were found. Constipation, rectal pain, and temporary urine or fecal incontinence were the main adverse effects.[12] One study identified as many as 20 articles discussing the use of BoNTA in PFM dysfunction. The most injected sites were the levator ani muscles. Success rates varied between 62 and 100 % [13]. Botox is a safe drug when used according to the manufacturer's recommendations [14].

More than half of the respondents were patients who had been married for 0-2 years. Another study showed that problems among couples who are unable to have natural sexual intercourse and vaginal penetration are considered unconsummated marriages. After 6 years, the couple's main problems are vaginismus and post-traumatic stress. [15]. The important risk factors for vaginismus were duration of marriage, sexual intercourse frequency, sexual satisfaction, marital satisfaction, and consensus. [16]. In marriage, treatment must involve two people, namely a man and a woman. One study examined interventions in couples. The average age of women is 29.5 years, and men is 32 years. The average length of marriage is more than 5 years. The FSFI score has increased. The couple is getting a therapy session. During a 30–45-minute pre-treatment consultation session, anxiety and fear and avoidance models of vaginal penetration were debated, considering the participants' individual beliefs, behaviors, and emotions. At the first visit, the therapist allows examination of the external genitalia. Neither of them allowed a complete vaginal examination (finger penetration) due to pelvic floor contractions at the first visit. Examination was carried out after informed consent. A couple has a private consultation session. The number of sessions was estimated between 4 to 6 sessions, and the duration of each session was 45-60 minutes. [17].

The results of the assessment of patient characteristics showed that almost all patients were of reproductive age, namely 20-35 years, were diagnosed with vaginismus, and received VT procedures. Female sexual function declines with age. This decline starts in the late 20s to the late 30s. Desire, frequency of orgasms, and frequency of intercourse decrease with age. The prevalence of most sexual difficulties or dysfunctions changes little with age, except for sexual pain, which may decrease.[18] The most frequently reported

problems in middle-aged women are vaginal dryness and dyspareunia. Dyspareunia, but not vaginal dryness, is associated with decreased frequency of intercourse during the climacteric period.[19]

Complaints related to sexual function among patients vary in severity. According to various statistics, between 4.2% and 42% of women of childbearing age report experiencing mild to severe sexual dysfunction. A study involving 258 patients diagnosed with vaginismus found that the mean maternal age was 29.2 ± 4.7 years. Among these patients, 86.86% had experienced at least one pregnancy and childbirth. The rate of caesarean delivery among treated individuals with vaginismus was comparable to that of the general population. Furthermore, vaginal delivery following treatment for vaginismus appears to be safe, with no observed increase in perineal morbidity or recurrence of the condition [4].

The limitation of this research is that it has not been able to explore deeply into patient complaints and management. Recommendations for further research are to examine patient experiences in depth regarding vaginismus treatment.

CONCLUSION

Case analysis shows that each patient has their own characteristics, so they require treatment according to the problem. Management in the study of Vaginismus requires cross-professional collaboration, such as psychiatrists and andrologists. The treatment given also tends to be complex.

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Research Article

A Mixed-Methods Evaluation of an Iron Supplementation Program for Adolescent Girls in Magelang City

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Abstract

Objective: To evaluate the implementation of the iron supplementation program for adolescent girls in Magelang City and identify supporting and inhibiting factors.

Methods: This study used a mixed-methods triangulation design with purposive sampling. Quantitative data from the Magelang City Health Office were analyzed descriptively, while qualitative data from interviews and FGDs explored implementation barriers.

Results: The program achieved 72.2% coverage, meeting the national target. Supporting factors included regulatory planning, digital reporting via e-PPGBM, cross-sectoral collaboration, and the Aksi Bergizi initiative. However, barriers such as lack of budget, SOPs, human resources, and low adherence were identified.

Discussion: Quantitative findings provided an overview of program success, while qualitative insights revealed operational challenges. Low adherence was influenced by limited awareness, unclear benefits, and perceived barriers like nausea and lack of parental support. Reporting delays and system closures also hindered performance.

Conclusion: Despite meeting coverage targets, the program faces significant implementation challenges. Strengthening budgeting, SOPs, and human resources, along with improving adolescent awareness, is essential for future success.

Keywords: Adolescent girls, iron supplementation, mixed-methods study, program evaluation.

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INTRODUCTION

The Indonesian government is trying to reduce stunting rates with the Accelerated Stunting Reduction Programme with specific and sensitive nutrition interventions, one of which is the iron supplementation tablet programme for adolescent girls [1]. The government's programme is in line with the World Health Organization's (WHO) Sustainable Development Goals (SDGs) with the aim of ending all malnutrition conditions in the world, including reducing stunting rates by providing adequate nutrition to adolescent girls[2]. The prevalence of anemia in pregnant women and adolescent girls in the South East Asia region is around 40% and a report from the Indian Council Medical Research (ICMR) states that anemia in adolescent girls is around 90% with severe anemia conditions around 7% [3]. The 2018 -Riset Kesehatan dasar (Riskesdas)- Basic Health Research survey reported the prevalence of anemia in the young age group to be 48.9% [4]. Iron deficiency anaemia is a condition where the body lacks iron in red blood cells below value 12 g/dL [5]. Adolescent girls are a group that requires high iron intake for physical growth, and

sexual needs such as menstruation [4,6]. Anemia in adolescent girls continues into pregnancy will experience maternal anemia. The main causes of maternal anemia in developing countries are iron deficiency, inadequate intake and infection [5].The adverse effects of anemia in pregnancy will cause complications in the mother and baby, namely post partum hemorrhage, prematurity, low birth weight babies and stunted growth [6,7,8]. Growth restriction in the prenatal child and short babies are major predictors of stunting at birth [9,10]. The incidence of stunting at birth which if not immediately corrected will continue to have a negative impact on long-term physical and intellectual growth in children [11].

WHO has advised all countries to reduce anaemia rates by 50% in adolescent girls or women of childbearing age by recommending iron supplementation where anaemia rates are more than 20%, including Indonesia [2,12]. Earlier investigations have identified several personal barriers to adherence, including fear of side effects, limited awareness of the benefits of iron tablets, misconceptions that iron tablets serve as contraceptives, and insufficient knowledge about their proper use [13]. Randomised trials have shown that intermittent iron supplementation given orally either daily or weekly has smilar effectiveness with fewer side effects and good compliance [12].

Despite iron deficiency is a recognized contributor to stunting, many interventions predominantly target younger children or pregnant women. Efforts to mitigate iron deficiency anemia have predominantly focused on supplementation-based interventions [14]. Interventions to address iron deficiency anemia include the administration of iron tablets, combined iron and folic acid (IFA) supplements, iron in combination with other micronutrients, as well as culturally tailored approaches such as the use of iron-fortified lentils. [13,15,16,17]. Non-supplementation interventions may be implemented through education and training programs [18,19]. Additionally, a combined approach involving supplementation and health promotion interventions may be implemented [20].

Magelang City is one of the cities located in Central Java Province of Indonesia with the second smallest area in Indonesia. Data from 2021 to 2022 indicate an upward trend in the stunting rate, increasing by 0.6% from 13.3% to 13.9%. Additionally, the prevalence of anemia among adolescent girls in Magelang City reached 43% in 2023, a figure approaching the national average. Despite a good Human Development Index (HDI), adequate access to health services and transportation, and the implementation of an iron supplementation program targeting adolescent girls, a thorough evaluation of the program's implementation in accelerating stunting reduction has yet to be conducted [1,21,22,23].

The substantial gap in anemia prevalence among adolescent girls necessitates a comprehensive evaluation. This study employs a mixed-methods approach focusing on program implementers to assess program outcomes and implementation by identifying facilitating and inhibiting factors, thereby informing alternative solutions. It can uncover sociocultural factors, logistical challenges, and individual perceptions influencing adherence—insights that quantitative studies alone cannot provide. Understanding these aspects is critical to evaluating the implementation of supplementation programs among adolescent girls [24,25].

METHODS

Ethical statement

This study received ethical approval from the Ethics and Research Commission of FK-KMK UGM on March 22th, 2024, under approval number KE/FK/0454/EC/2024. Prior to data collection, permission was obtained from the Magelang City Government through letter number 070/ IV.194/330/2024. Participants were fully informed about the research procedures, and their participation was voluntary, with the option to withdraw at any time without any consequences. Confidentiality was strictly maintained, ensuring that participants' employment status and residential locations were not disclosed or affected. After completing the interviews, the researchers thanked the participants and offered tokens of appreciation, including transportation allowances and gifts.

Study design

This study employed a mixed-methods design with a concurrent triangulation approach to achieve a comprehensive understanding and formulate alternative solutions. The quantitative component assessed the role of program implementers in achieving iron supplementation

coverage among adolescent girls, based on secondary data from the Magelang City Health Office, analyzed descriptively. The data did not include individual characteristics or clinical outcomes. The qualitative component was obtained through in-depth interviews and focus group discussions, focusing on the experiences of program implementers. Beneficiaries were involved only to validate program implementation. The study did not directly assess stunting prevention, which is considered a long-term outcome of iron supplementation and was discussed only in the introduction.

The qualitative assessment was guided by the Donabedian framework, which includes three key aspects: input, process, and output. The input aspects evaluated comprised regulations, budget allocation, human resources, facilities, and planning. The process aspects included the implementation of standard operating procedures (SOPs), reporting mechanisms, and monitoring activities. The output aspect focused on identifying supporting and inhibiting factors affecting program implementation. Data were collected through recorded in-depth interviews, transcribed verbatim using Microsoft Excel, and thematically categorized based on the input-process-output structure of the Donabedian model [26]. Qualitative data were interpreted to identify root causes and propose alternative solutions. Data collection and analysis were conducted by a team of four researchers, including the principal investigator—an experienced specialist in Obstetrics and Gynecology—supported by one trained research assistant who had received prior instruction on assisting with the study.

Participant

Participants in the quantitative component of this study were drawn from the 2024 registry data of the Magelang City Health Office, which recorded a total of 13,574 adolescent girls, of whom 9,801 had received iron supplementation. The data focused on junior high school students in grade 7 and senior high school students in grade 12, as reported by five main primary health care in Magelang City: South Magelang, Jurang Ombo, Central Magelang, Kerkopan, and North Magelang. However, the data were limited to the distribution of iron supplement tablets and did not include classifications by age, educational level, menstrual history, hemoglobin levels, or other relevant characteristics.

The qualitative component involved purposive sampling, consisting of eight program implementers who participated in in-depth interviews. Additionally, 17 participants took part in three focus group discussions (FGDs). FGDs 1 and 2 were conducted with five coordinating midwives and five primary health care volunteers (cadres) from the main primary health care, while FGD 3 involved one representative beneficiary from the Central Magelang sub-district.

Data collection

This study was conducted in Magelang City, Central Java Province, Indonesia, beginning in April 2024. Quantitative data collection commenced after obtaining informed consent from eight key stakeholders responsible for the iron supplementation program targeting adolescent girls. These participants included the Head of *Dinas Kesehatan Kota (DKK)* – City Health Office, representatives from *Dinas Pemberdayaan Masyarakat dan Perlindungan Perempuan dan Anak, Pengendalian Penduduk, dan Keluarga Berencana (DPMP4KB)* – Office of Women's Empowerment, Child Protection, Population Control and Family Planning, – *Badan Perencanaan dan Penelitian Daerah (BAPERIDA)* – Regional Research and Planning Office, – *Badan Kependudukan dan Keluarga Berencana Nasional (BKKBN) Jawa Tengah* – National Population and Family Planning Office, Central Java staff, – *Usaha Kesehatan Sekolah (UKS)* – School Health, the Head of – *Kesehatan Keluarga (Kesga)* – Family Health team, and program implementers at the health office.

Data collection involved both primary and secondary sources. Secondary data for the quantitative component were obtained from the registry of the Magelang City Health Office. Primary data for the qualitative component were collected through in-depth interviews, followed by three sessions of Focus Group Discussions (FGDs) to enrich and validate the findings.

Sampling method

In this study, participants for the qualitative component were selected using purposive sampling, based on specific criteria established by the researchers. Eligible participants included individuals responsible for or directly involved in implementing the iron supplementation

program, actively engaged in the stunting reduction acceleration team, and working within the Magelang City area. A representative of the program beneficiaries was also included, selected from the Central Magelang region, which serves as the designated stunting locus.

Reflexivity

To reduce bias in data collection, reflexivity was upheld by the principal investigator—an experienced Obstetrics and Gynecology specialist unaffiliated with stakeholder agencies. Participants were assured of confidentiality and professional neutrality, with informed consent obtained prior to interviews. The investigator, professionally engaged in Social Obstetrics, was supervised by senior specialists from Gadjah Mada, Diponegoro, and Sebelas Maret Universities, and assisted by a trained nutritionist with field experience

RESULTS

Quantitatif Study

The quantitative results are presented descriptively, including demographic characteristics, data from in-depth interviews and Focus Group Discussions (FGDs 1, 2, and 3), and the achievement of national targets, as shown in Tables 1, 2, and 3.

Table 1. Characteristics of informants in the in-depth interviews of dinas level implementers

Variable	Characteristics	n	%
Gender	Male	3	37
	Female	5	63
	Total	8	100
Age (Years)	<50	5	63
	>50	3	37
	Total	8	100
Education	College of Health	4	50
	Non-Health Colleges	4	50
	Total	8	100
Occupation	<5	1	13
	>5	7	87
	Total	8	100

Regarding **Table 1** the demographic characteristics of the in-depth interview informants, the majority were female, approximately 50 years old, and held a university degree.

Table 2. Characteristics of FGD 1, 2, and 3 informants

Variable	1st FGD N (%)	2nd FGD N (%)	3th FGD N (%)
Age			
- <50	4 (80)	2 (40)	7 (100)
- >50	1 (20)	3 (60)	
Education			
- Secondary Primary School		4(80)	7(100)
- Non-Health Colleges		1(20)	
- College of Health	5(100)		
Occuppation			
- Not working			6(86)
- <10 tahun		2(40)	1(14)
- >10 tahun	5(100)	3(60)	

As shown in this table, most informants are less than 50 years old, while FGD 1 informants all have a tertiary education in the health sector. FGDs 2 and 3 mostly have secondary education. The length of employment in FGDs 1 and 2 is above 5 years, while FGD 3 is mostly unemployed **(Table 2)**.

The distribution of iron supplementation among adolescent girls in the five main primary health care in Magelang City. In 2023, approximately 72.2% of 13,574 adolescent girls received iron supplementation through a regional health program. However, the distribution across the working areas was uneven, with the North and Central areas showing higher coverage. Several other areas-including one sub-district with no recipients-indicate gaps in program implementation that require targeted improvements. Overall, the iron supplementation program for adolescent girls in Magelang City has exceeded the national target, achieving a coverage rate of 72.2% compared to the national standard of 58%.[27].

Qualitative Study

Table 3. Qualitative Results Findings

Framework Donabedian	Supporting factors	Inhibiting factors
Input	The existing regulation and planning available (I6 Stakeholder) Sufficient facilities (I5 Stakeholder)	None of Special budget and Standard Operating Procedure (I6 Stakeholder) Lack of human resources (I5 Stakeholder)
Process	EPPGBM application report (Stakeholder I6).	Inadequate monitoring (I20 Beneficiaries)
output	Innovative program "Aksi Bergizi" (I3 Stakeholder), (I9 Stakeholder)	Medication adherence and bored (I8 Stakeholder) Dislike eating vegetables (I7 Stakeholder) Feel nauseous and dispose tablets (Cadres I15)

The table presents interview excerpts from stakeholders, health cadres, and beneficiaries, highlighting key enablers and barriers to program implementation based on the Donabedian framework. Supporting factors include regulatory planning, digital reporting through *Elektronik-Pencatatan dan Pelaporan Gizi Berbasis Masyarakat* (EPPGBM), a Community-Based Nutrition Reporting Application, and the Aksi Bergizi initiative. Barriers include the absence of a dedicated budget, lack of standard operating procedures (SOPs), insufficient monitoring, and individual challenges such as poor adherence, nausea, and aversion to vegetables (Table 3).

Table 4. The theme of barriers to the implementation of iron supplementation program for adolescent girls in Magelang 2023

Theme	Stakeholder	Caders	Beneficiaries
Budget	Special budget none (I7), (I8)		
Human Resources	insufficient number and capacity of human resources (I1), (I3), (I5), (I6), (I8)		
SOP	No SOPs (I1), (I3), (I4), (I6) Difference in the amount of tablet given (I6), (I8)	Difference in the amount of tablet given (I14), (I15), (I16), (I17), (118)	Difference in the amount of tablet given (I20)
Monitoring	lack of supervision and monitoring (I1), (I3), (I7), (I8)	lack of supervision and monitoring (I5), (I16), (I17), (I18)	lack of supervision and monitoring (I27)
Side Effects and Adherence	Medication non-adherence (I6)	medication non-adherence and nausea (I15), (I17) throw the tablets away (I15)	medication non-adherence (I20),(I27)

The following table presents the barriers to the implementation of the iron supplementation program for adolescent girls in Magelang in 2023. The interview quotes are grouped based on the information provided by stakeholders, caders, and beneficiaries regarding barriers to program implementation. The grouping aims to increase the trustworthiness of the data **(Table 4)**.

Table 5. Joint Display Table

Evaluation Aspect	Quantitative Results	Qualitative Results	Interpretation	Solution
Program Achievement (Output)	72.2% of adolescent girls received iron tablets (above the national target of 58%)	"Aksi Bergizi" implemented every Friday at schools; tablets are distributed by teachers	The program is administratively implemented, but actual consumption and adherence cannot be guaranteed.	Provide SOPs
SOP and Technical Guidelines (Process)	No data available	No formal SOP available; implementation only refers to the terms of reference (I6)	The absence of a clear SOP results in inconsistent implementation and weak quality control.	Provide SOPs
Monitoring and Evaluation (Process)	No post-program Hb data available	Hb is only screened initially; no follow-up Hb checks (I20)	Lack of biological outcome evaluation makes it difficult to measure program effectiveness.	improved monitoring system and data usage
Side Effects and Adherence (Output)	No data available	Students report boredom, nausea; some throw the tablets away (I15, I8)	Side effects are a major barrier to adherence; tablet distribution does not ensure actual intake.	Quality of iron supplement Provide SOPs
Cross-Sector Support and Coordination (Input)	No data available	Special circular letter from mayor and annual government planning exist (I6, I8)	Policy support exists but lacks corresponding funding and capacity-building for implementers.	capacity-building and budgeting
Role of Teachers and Parents (Process & Output)	No data available	Teachers see themselves as mere distributors; parents are not involved (I8)	Monitoring is weak due to limited involvement of key actors such as teachers and parents.	Coordination stakeholder, school and parent.

This report integrates findings from the quantitative and qualitative research, presenting key themes identified in the program implementation evaluation along with potential alternative solutions. These themes include Program Achievements, Standard Operating Procedures (SOPs) and Technical Guidelines, Monitoring and Evaluation, Side Effects and Compliance, Cross-Sector Support and Coordination, and the Role of Teachers and Parents.

DISCUSSION

This study employed a mixed-methods approach, using quantitative data to assess program coverage and qualitative data to explore implementation barriers from the implementers' perspective. The iron supplementation program for adolescent girls in Magelang City achieved a coverage rate of 72.2%, which could have been higher without reporting delays. Magelang Selatan Primary Health Care was unable to enter data into the community-based nutrition reporting application (EPGBM) due to system closure.

This study, using a mixed-methods approach, found that while quantitative data showed general program coverage, qualitative findings revealed deeper implementation challenges. Despite supportive elements like regulations, digital reporting (EPPGBM), cross-sectoral collaboration, and the *Aksi Bergizi* initiative, barriers persist. These include lack of dedicated budget, insufficient human resources, absence of SOPs, inconsistent supplementation standards, weak monitoring, and low knowledge and adherence among adolescent girls. Reporting delays further underscore the need for targeted improvements in future program implementation.

These challenges can be resolved by allocating a dedicated budget and strengthening human resources. Given the program's role in preventing anemia among adolescent girls, specific funding and adequate personnel are essential for effective implementation. Availability should be evaluated in terms of both quantity, ensuring

sufficient personnel, and quality, assessed based on skills, educational background (minimum a health-related degree), experience, certification, and dedication [28].

Standard Operating Procedures (SOPs) are essential to prevent miscommunication and misinterpretation in the field (Table 6). SOPs provide detailed guidelines outlining the steps required to carry out activities or programs consistently, efficiently, and in accordance with established standards, thereby minimizing errors [29]. Discrepancies between the quantity of iron supplements distributed and those received by beneficiaries can be addressed by implementing SOPs for receiving, storing, and administering iron supplements, which specify dosage and scheduling.

Issues related to inadequate monitoring at primary health care and schools can be mitigated through the development of monitoring and evaluation SOPs, alongside SOPs for examination and screening of adolescent girls. To address challenges concerning side effects and adherence among adolescent girls, SOPs for education and counseling of adolescents and parents, management of side effects, and reporting and documentation have been established. Additionally, improving the quality of iron supplements, such as providing sugar-coated tablets, may enhance adherence and reduce side effects[29].

Low adherence to iron supplementation among adolescent girls in Magelang, as explained by the Health Belief Model (HBM), stems from limited awareness of anemia risks and unclear understanding of its severity and benefits. Barriers such as nausea, boredom, skipped meals, and lack of parental support further discourage compliance. Although external cues to action, such as the weekly school-based "Aksi Bergizi" program, are in place, these interventions alone are insufficient without fostering internal motivation[30]. Furthermore, low self-efficacy among both adolescents and teachers who often feel responsible only for distribution, not follow-through hampers consistent consumption. Addressing these issues requires strengthening health education, reducing barriers (e.g., managing side effects and food availability), involving parents more actively, and enhancing motivation and confidence through tailored communication and supportive systems [18].

A similar program implemented in Vietnam in 2006, which provided weekly iron–folic acid supplementation in combination with anti-helminthic treatment, demonstrated a significant reduction in anemia prevalence—from 37.8% to 14.3% over a six-year period. These findings suggest that sustained weekly iron and folic acid supplementation, when integrated with anti-parasitic interventions, is a practical and effective strategy for reducing anemia among women of reproductive age [31]. Layrea (2023) evaluated the GIFT Program in Accra and found that adherence to protocol supported its success, while low motivation, side effects, and misconceptions such as fears that IFA supplements affect fertility were key barriers. The study recommends improving supplement quality and community awareness to enhance program outcomes [32].

Strengths and limitations

This preliminary study in Magelang City provides useful insights for evaluating small-scale programs in areas with unique geographic and health service contexts, especially within Indonesia's stunting reduction efforts. While it offers a thorough review of program implementation and achievements, limitations such as missing individual data and potential stakeholder bias restrict its ability to assess overall impact. The findings mainly highlight implementation challenges rather than program success.

CONCLUSION

Although the iron supplementation program for adolescent girls has reached the national target, challenges remain in Magelang, including limited budgets, human resources, SOPs, monitoring systems, supplement quality, and cross-sector collaboration. Addressing these requires improvements in capacity building, budgeting, stakeholder coordination, SOP development, data systems, and supplement quality. Future research should explore factors affecting implementation and consider cluster-randomized controlled trials to assess the impact of educational and behavior change interventions. Sustainable reductions in adolescent anemia and stunting will depend on multilevel collaboration, evidence-based planning, and long-term behavior change strategies.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in this research

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Attachment:

Informant Data Table from In-Depth Interviews and Focus Group Discussions

Code	Age	Education	Duration of Work	Origin of agency	Department	Position In Program
I1	46	Economics degree	27 year	BAPERIDA	Governance and Human Development	Stakeholder
I2	54	Master of health management	32 year	DPMP4KB	Head of Department DPMP4KB	Stakeholder
I3	44	Doctor	18 year	DKK	Head of DKK	Stakeholder
I4	25	law degree	3 year	BKKBN Central Java Province	Technical Assitant BKKBN Magelang City	Stakeholder
I5	42	Nutritions degree	15 year	DKK	Programme implemetation	Stakeholder
I6	45	Master of public health	21 year	DKK	Head of the family welfare team	Stakeholder
17	53	Master of health management	31 year	Education and Culture Office	Head of Department	Stakeholder
I8	56	Bachelor's degree in biology	26 year	Junior High School 2 Magelang City	Student health unit teacher	Stakeholder
I9	42	D4 Professional midwife	11 year	North Magelang Primary Health Care (PHC)	Midwife Supervisor	Stakeholder
I10	42	D4 Professional midwife	19 year	Kerkopan PHC	Midwife Supervisor	Stakeholder
I11	32	D3 Midwifery	32 year	Central Magelang PHC	Midwife Supervisor	Stakeholder
I12	41	D3 Midwifery	19 year	South Magelang PHC	Field Midwife	Stakeholder
I13	51	D4 Professional midwife	31 year	Jurangombo PHC	Midwife Coordinator	Stakeholder
I14	55	Senior high school	10 year	North Magelang PHC	North Magelang PHC cadres	Cadres
I15	43	Senior high school	7 year	Kerkopan PHC	Kerkopan PHC cadres	Cadres
I16	51	Senior high school	11 year	Central Magelang PHC	Central Magelang PHC cadres	Cadres
I17	52	Bachelor 1	4 year	Jurang ombo PHC	Central Magelang PHC cadres	Cadres
I18	44	Vocational high school	2,5 year	South Magelang PHC	South Magelang PHC cadres	Cadres
I19	29	Vocational high school		Housewife		Beneficiaries
I20	14	junior high school		Students		Beneficiaries
I21	22	junior high school		Housewife		Beneficiaries
I22	28	Vocational high school		Housewife		Beneficiaries
I23	22	Senior high school		Housewife		Beneficiaries
I24	24	Vocational high school		Shopkeeper		Beneficiaries
125	16	Senior high school		Housewife		Beneficiaries

Research Article

Feasibility Study of Integrated Service for Congenital Abnormalities in A Low-Middle Income Country

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Abstract

Background: Congenital abnormalities are anatomical and physiological abnormalities that are present in fetus. One of the main causes of high infant mortality and neonatal mortality in Indonesia is congenital abnormalities in fetus. This study describes the prevalence of congenital abnormalities in Dr. Cipto Mangunkusumo Hospital, as a tertiary referral hospital in Indonesia, which would further require integrated healthcare services on a better management for a favorable outcome in babies.

Methods: All the data were collected within one-year of prenatal screening in Dr. Cipto Mangunkusumo General Hospital, resulting in 323 patients. The data were further analyzed in retrospective cohort study. Collected data includes the information such as, patients' age, birth date, reproductive history, gestational age, and congenital abnormalities of the baby.

Results: The data shows that patients with the age group of 30-39 years old dominated the cases of pregnancy with congenital abnormalities. Cases are also more dominant in the gestational age of 13 – 28 weeks (second-trimester). Most cases of abnormalities are from the central nervous system with 159 cases and followed by the cardiovascular system with 130 cases. Overall the prevalence of congenital abnormalities detected within patients during prenatal screening in Dr. Cipto Mangunkusumo General Hospital are 607 cases from 494 patients.

Conclusion: This study highlights the prevalence of congenital abnormalities found in Dr. Cipto Mangunkusumo Hospital within a year. These findings highlight the need for timely, well-organized prenatal screening and coordinated care, especially in referral hospitals. Improving early detection and management can help ensure better outcomes for both mothers and babies.

Keywords: birth defect, congenital abnormalities, prenatal screening.

Correspondence Author.

INTRODUCTION

Congenital abnormalities are structural or functional anomalies that develop during intrauterine life and are present at birth. One of the leading causes of high infant mortality in Indonesia is congenital abnormalities in babies.[1] The data for infant mortality rate in Indonesia is estimated at 32 cases per 1000 live births, while neonatal mortality rate stands at 19 cases per 1,000 live births. According to the World Health Organization (WHO) South-East Asia Region, the prevalence of congenital abnormalities in Indonesia is happening around 59.3 cases per 1,000 live births. With an estimated of 5 million births annually, this translates to around 295,000 cases of congenital abnormalities each year.[2,3] Apart from causing neonatal deaths, congenital abnormalities are also causes of stillbirths and spontaneous abortions in pregnancy. If the baby survives, the baby will become disabled or suffer from chronic diseases. Integrated treatment is

needed to detect congenital abnormalities in babies early-on, so that appropriate management can be carried out to ensure the prevention of infant morbidity and mortality.[4]

The etiology of congenital abnormalities are multifactorial, including genetic abnormalities, infections, and environmental factors. Prevention strategies such as vaccination, adequate folic acid and iodine intake, avoidance of teratogenic substances (e.g., alcohol), and promotion of a healthy maternal lifestyle—are known to reduce the risk of these anomalies. Mothers with a history of alcohol consumption, cigarette smoke exposure, multiparity, older age, drug consumption, consanguinity, previous history of children with congenital abnormalities, family history of congenital abnormalities, low economic status, gestational diabetes, and history of abortion or miscarriage are all factors that increases the occurrence of congenital abnormalities in the fetus during pregnancy.[5]

At Dr. Cipto Mangunkusumo Hospital, a tertiary referral center in Indonesia, congenital and fetal abnormalities are identified across nearly all organ systems. Each month, tens to hundreds of new cases are reported among pregnant women undergoing prenatal screening at the hospital's fetomaternal outpatient clinic. This study aims to examine the spectrum of congenital abnormalities detected in fetuses at Dr. Cipto Mangunkusumo General Hospital and to advocate for the importance of integrated services from early screening to targeted intervention. Prenatal screening using fetomaternal ultrasound plays a pivotal role in the early identification of fetal anomalies. Routine prenatal ultrasound has been shown to reduce neonatal mortality, particularly by enabling timely detection of congenital heart defects. Postnatal neonatal screening is also essential for detecting abnormalities that may not have been visible during pregnancy.[6]

In Indonesia, the practices of neonatal screening face several challenges and obstacles, such as lack of prevalence data, ethical concerns, insufficient family engagement, shortages of trained health personnel, and the lacks of standardized programs and professional training for healthcare providers.[7] Management strategies for congenital abnormalities vary depending on the condition and may include pharmacologic interventions, such as corticosteroids, or surgical procedures, such as spina bifida repair.[1] This research aims to provide comprehensive data and insights on the prevalence and spectrum of congenital abnormalities diagnosed at Dr. Cipto Mangunkusumo General Hospital over a one-year period. By delineating the burden and characteristics of these conditions, we seek to support the development of better-integrated, multidisciplinary services for the management of congenital abnormalities. In parallel, this study also serves as a feasibility assessment for the implementation of a structured birth defect management program, evaluating the clinical, logistical, and ethical dimensions of care delivery. Through this dual approach, we aim to inform future policy and practice in optimizing outcomes for affected neonates and their families.

METHODS

This retrospective cohort study was conducted using data from 323 samples of pregnant patients treated in Dr. Cipto Mangunkusumo General Hospital in a year, starting from March 2023 to March 2024. The data was obtained from the patients' electronic health records at the out-patient fetomaternal and high-risk pregnancy clinic. This study describes the prevalence of patients carrying babies with congenital abnormalities during pregnancy. Congenital abnormalities are diagnosed in the first, second, and third trimester of pregnancy by using fetomaternal ultrasonography. The abnormalities are then divided into several groups such as disorders of the central nervous system, face, thorax, heart, abdomen, extremities, genitals, syndromes, and others. We started analyzing maternal variables such as maternal age and gestational age. In order to ensure the accuracy and relevance of the data, specific inclusion and exclusion criteria were applied when selecting patient records for analysis.

Subject Criteria

Inclusion criteria:
1. Pregnant women aged ≥18 years.
2. Diagnosed with fetal congenital abnormalities at Dr. Cipto Mangunkusumo General Hospital between March 2023 and March 2024.
3. Provided informed consent for the use of their medical data in this study.
4. Data collected during the patient's first visit.

Exclusion criteria:
1. Pregnant women aged <18 years.
2. Data collected from follow-up visits and not

the initial consultation.
3. Duplicate records of the same patient.
4. Absence of congenital abnormalities in the fetus.
5. Patients were treated or received management on placenta accreta spectrum (PAS) at Dr. Cipto Mangunkusumo General Hospital before July 2020 or after February 2024.
6. Data that were not approved for research use.
7. Duplicate datasets.

Sample Size Determination

To obtain a comprehensive dataset, total sampling was employed. All obstetric patients examined at the Fetomaternal Clinic of Dr. Cipto Mangunkusumo General Hospital between March 2023 and March 2024 were included, provided they met the inclusion criteria.

Procedures and Data Collection

To obtain relevant clinical information, patient data were collected from electronic medical records of those who underwent fetomaternal ultrasonography at their first clinic visit. All ultrasound examinations were performed as part of routine diagnostic evaluation at Dr. Cipto Mangunkusumo General Hospital. Only the initial consultation data were used to avoid duplication or confounding from follow-up evaluations. The collected data were then entered into a structured database for further analysis.

Study Parameters

The parameters assessed in this study followed a descriptive-analytic approach. The research utilized secondary data from pregnant patients carrying fetuses diagnosed with congenital abnormalities. Only first-visit data were considered, with particular attention to gestational age, maternal age, and the type of congenital abnormality diagnosed.

Data Analysis and Statistical Methods

For the purpose of statistical evaluation, the study was conducted following ethical approval from the Ethics Committee of the Faculty of Medicine, Universitas Indonesia and Dr. Cipto Mangunkusumo Hospital. All extracted data were organized into tables and analyzed using SPSS statistical software. Descriptive statistics were used to summarize the distribution and frequency of congenital abnormalities, while appropriate analytical methods were employed to explore associations among clinical variables.

Ethical Approval

This study is a retrospective study using secondary data from medical records at Dr. Cipto Mangunkusumo Hospital. We used a total sampling method for patients examined at the Dr. Cipto Mangunkusumo Hospital fetomaternal polyclinic between March 2023 and March 2024. The study was conducted after being considered ethically feasible by the ethics committee of the Faculty of Medicine, University of Indonesia or RSCM. The data taken were then entered into a table for statistical analysis. Data for each patient will be collected through procedures in accordance with ethical regulations, and will be kept confidential. Data will be stored on file and will not be shown to unauthorized parties. The identities of patients in the study were not published or presented.

RESULTS

Table 1. Maternal Age and Gestational Age Distributions

	Variable	n	Percentage (%)
Age	≥18	131	40.6
	≥30	154	47.7
	≥40	38	11.8
Gestational age	Trimester 1	131	40.6
	Trimester 2	154	47.7
	Trimester 3	38	11.8

The data presented in table 1 shown above are samples from inpatients at Fetomaternal and High-Risk Pregnancy Clinic in Dr. Cipto Mangunkusumo General Hospital. Table 1 outlines the maternal and gestational age characteristics from the study samples. The maternal age groups were divided into three categories based on evidence from previous research, which indicates an increased risk of congenital abnormalities beginning in the 30s and a notably high risk in mothers aged 40 and above.8 In this study, the age group of mothers carrying the most fetus with congenital abnormalities is 30- 39 years old group with the percentages of 47.7%, followed by the 18-29 years old group with the per percentages of 40.6%, lastly 40 and above with the percentages of 11.8%. The most cases of congenital defects

found in the second-trimester, around 47.7%.

In this research, A total of 607 congenital abnormality cases were identified among 494 patients, indicating that multiple anomalies were present in some individuals. Table 2 presents the distribution of congenital abnormalities by anatomical system, based on both total cases and total patients, from the inpatient cohort at the Fetomaternal and High-Risk Pregnancy Clinic of Dr. Cipto Mangunkusumo General Hospital. The highest occurrence of congenital defects cases were found in the central nervous system, accounting for 26.2% of total cases and 26.7% of total patients. Within this category, central nervous system (CNS) anomalies were predominant (26.2% of cases; 132 patients), followed by facial structure abnormalities (9.4% of cases). Cardiovascular anomalies were the second most common, comprising 21.4% of all cases and affecting 16.8% of patients, underscoring the critical burden of congenital heart defects.

Table 2. Congenital Abnormalities Distribution of Total Patient and Cases

Variable		Total Cases	(%)	Total Patient	(%)
Head and Neurological System	CNS	159	26.2	132	26.7
	Facial Structure	57	9.4	44	8.9
Cardiorespiratory System	Respiratory	9	1.5	8	1.6
	Cardiovascular	130	21.4	83	16.8
Gastrointestinal System	Abdominal	53	8.7	51	10.3
	Urogenital	52	8.6	46	9.3
Syndrome	Syndrome	22	3.6	22	4.5
Others	Extremities	41	6.8	38	7.7
	Others	84	13.8	70	14.2
TOTAL		607	100	494	100

Abdominal and urogenital abnormalities were relatively balanced, contributing 8.7% and 8.6% to the total cases, respectively. Abnormalities involving extremities and syndromes were also notable, representing 6.8% and 3.6% of cases. The "syndrome" category refers to a group of congenital abnormalities characterized by a consistent and recognizable pattern of anomalies that stem from a common underlying cause, which may be genetic, environmental, or pathophysiological in origin.[9,10] This includes classical syndromes such as chromosomal or genetic disorders, as well as specific fetal conditions with syndromic presentations such as Potter sequence, typically resulting from severe oligohydramnios and renal agenesis and twin-to-twin transfusion syndrome (TTTS), particularly as classified by the Quintero staging system, which describes progressive hemodynamic imbalance between monochorionic twins.[9,10] These conditions are grouped separately from isolated structural anomalies due to their multi-system involvement and complex pathogenesis. The "Others" category, which included various anomalies not categorized under the main systems, accounted for 13.8% of cases and affected 14.2% of patients highlighting the heterogeneity and diagnostic complexity of congenital disorders.

Overall, the data suggest a high prevalence of central nervous system and cardiovascular anomalies among the studied population, which aligns with global epidemiological patterns. The findings underscore the importance of early screening and multidisciplinary management strategies for congenital anomalies in tertiary referral settings.

DISCUSSION

Integrated maternal-fetal care is essential in optimizing outcomes for both mother and fetus, particularly in pregnancies complicated by congenital anomalies. Comprehensive care including systematic screening, accurate diagnosis, multidisciplinary management, timely therapeutic interventions, and close perinatal monitoring serves to mitigate perinatal morbidity and mortality.[11] Prenatal ultrasonography remains a cornerstone in the detection of fetal anomalies, facilitating early decision-making and enabling timely interventions that are associated

with improved neonatal outcomes. More than 50% of congenital anomalies can be identified antenatally, with early surgical correction significantly reducing associated morbidities and improving long-term prognoses.[11]

Recent advances in ultrasonography and fetal surgical techniques have substantially enhanced the prenatal diagnosis and management of structural anomalies. In specific indications such as fetal myelomeningocele or lower urinary tract obstruction (LUTO), in utero corrective surgery has demonstrated superior neonatal and neurodevelopmental outcomes compared to postnatal interventions.[12,13] The efficacy of these procedures is maximized when conducted in specialized referral centers equipped with multidisciplinary fetal medicine and pediatric surgical teams. This underscores the importance of centralized care models in managing complex fetal conditions.[12,13]

Despite many advancements being made, significant gaps persist in the current literature and healthcare systems. There is a lack of comprehensive national data on the prevalence and outcomes of specific congenital anomalies, which impedes effective health policy formulation.[7] Ethical dilemmas surrounding fetal interventions, limited public and familial awareness, and the scarcity of specialized perinatal healthcare professionals and formal training programs further constrain the delivery of optimal care.[1] Management strategies for congenital anomalies span a spectrum from pharmacologic therapy to highly specialized surgical procedures. For instance, obstructive uropathies such as posterior urethral valves and congenital renal tumors may necessitate early neonatal surgical intervention.[14] Central nervous system anomalies including hydrocephalus, encephalocele, and myelomeningocele are now frequently managed via neurosurgical approaches, either prenatally or postnatally, depending on severity and feasibility.[15]

Similarly, thoracic and gastrointestinal malformations, such as Congenital Cystic Adenomatoid Malformation (CCAM), Congenital Diaphragmatic Hernia (CDH), and intestinal atresias, often require staged surgical repair and comprehensive perioperative support.[16] Cardiac anomalies, including transposition of the great arteries and ventricular septal defects, have seen marked improvement in outcomes through corrective procedures such as the arterial switch operation and surgical closure of septal defects.[17] Non-surgical interventions also play a critical role in fetal and neonatal management. For example, antenatal corticosteroids are used to accelerate pulmonary maturation in fetuses with CDH, while postnatal support such as mechanical ventilation or Extracorporeal Membrane Oxygenation (ECMO) is often vital.[18] In cases of mild hydronephrosis, conservative management with routine surveillance and prophylactic antibiotics may be sufficient.[19] Conversely, in neonates with non-operable or syndromic congenital heart defects, medical stabilization, such as prostaglandin infusion and palliative care are often the mainstays of treatment.[20]

Nevertheless, certain anomalies remain fatal or incompatible with life. Conditions such as anencephaly, bilateral renal agenesis, and severe chromosomal disorders (e.g., trisomy 13 or 18) necessitate a shift in focus towards supportive and compassionate palliative care, aligning management goals with quality-of-life considerations and family-centered decision-making.[21]

Strengths and Limitations of the Study

This study draws upon a large, diverse cohort from a national referral center, allowing for meaningful analysis of congenital anomaly patterns across multiple organ systems. The integration of multidisciplinary clinical outcomes enriches the interpretability and applicability of the findings. However, several limitations must be acknowledged. The retrospective design limits the ability to establish causal inferences, and long-term follow-up data were not available for all cases, precluding comprehensive evaluation of developmental outcomes. Additionally, the absence of complete national prevalence statistics for specific anomalies highlights the need for more robust surveillance systems and registries.

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CONFLICT of INTEREST

Authors declare that they have no conflict of interests.

CONCLUSION

Amidst ongoing efforts to enhance outcomes for neonates with congenital abnormalities, there is a growing imperative to align clinical interventions with evidence-based criteria that prioritize both feasibility and long-term benefit. A comprehensive understanding of congenital anomaly prevalence is essential for optimizing neonatal care. At Dr. Cipto Mangunkusumo General Hospital, central nervous system anomalies were the most common (26.2%), followed by cardiovascular (21.4%), gastrointestinal, and urogenital defects (8–9%). These findings highlight the heterogeneity of cases in a tertiary referral center and underscore the need for integrated, multidisciplinary approaches that balance intervention feasibility with long-term outcomes.

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Research Article

Emotional Impact of In Vitro Fertilization (IVF): Anxiety, Depression, and Their Relationship with Pregnancy Outcomes

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Abstract

Objectives: To examine anxiety and depression experienced by women at different stages of IVF and to analyze their association with pregnancy outcomes.

Methods: This cohort study was conducted at Dr. Cipto Mangunkusumo General Hospital and Dr. Sander B. Daya Medika Clinic from May 2018 to March 2023. Data were collected using questionnaires and assessments during IVF, focusing on anxiety, depression, and pregnancy outcomes. Chi-square and Fisher's exact tests were used to assess associations between variables, while Friedman ANOVA was applied for longitudinal analysis of anxiety and depression scores across IVF stages.

Results: A total of 61 participants were included in the final analysis. Significant changes in anxiety and depression were observed throughout the IVF process. Both anxiety ($p < 0.001$, Kendall's $w = 0.19$) and depression ($p = 0.001$, Kendall's $w = 0.121$) levels increased significantly over time. A significant association was found between childbearing plans and anxiety ($p = 0.037$) at measurement II (before embryo transfer), as well as between education level and depression ($p = 0.038$) at measurement III (before pregnancy testing). However, no statistically significant association was observed between anxiety or depression scores and pregnancy outcomes across the three measurement points ($p > 0.05$).

Conclusion: Anxiety and depression significantly increase during IVF but are not associated with clinical pregnancy rates. These findings highlight the importance of mental health screening and psychiatric support during IVF to enhance women's comfort and help them navigate the process more effectively.

Keywords: anxiety, depression, in Vitro Fertilization (IVF), pregnancy outcomes, women.

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INTRODUCTION

Conception and reproduction serve as fundamental elements in the lives of many couples. Consequently, when a couple encounters difficulties in achieving spontaneous conception, both partners often experience profound sadness and disappointment. If conception does not occur after one year of consistent, unprotected intercourse, the couple is classified as experiencing infertility.[1] In 2021, the World Health Organization (WHO) indicated that the rate of infertility in high-income countries is 17.8%, whereas it is 16.5% in low- and middle-income countries.[2] In Indonesia, it is estimated that between 10% and 15% of women aged 15 to 45 experience infertility, which equates to around four to six million couples affected by both primary and secondary infertility.[3] This condition is a significant source of psychological stress, with anxiety and depression being the most prevalent psychological disorders among individuals facing infertility.[1]

Couples experiencing infertility often explore various avenues to achieve pregnancy, engaging in multiple evaluations and treatments in their pursuit of favorable outcomes. When alternative techniques, such as insemination, do not produce successful results, assisted reproductive technology (ART) becomes a viable option. In vitro fertilization (IVF), commonly known as the "test-tube baby" procedure, is a form of ART utilized after other methods have proven ineffective. The Centers for Disease Control and Prevention (CDC) indicates that the live birth rate following embryo transfer stands at 49.0% for women aged under 35, whereas this rate declines to 24.1% for women over the age of 40.[4,5] In Indonesia, 48.9% of women who participated in in vitro fertilization (IVF) were aged below 35 years. The success rates for pregnancies resulting from IVF procedures varied between 24.6% and 37.3%.[6]

Many couples with infertility who undergo assisted reproductive technology (ART) are at an increased risk of developing psychiatric disorders. High financial burden and uncertain efficacy of these treatments can impose considerable pressure on couples engaged in IVF.7 Research indicates that various stages of in vitro fertilization (IVF), such as hormone stimulation, ovarian stimulation, oocyte retrieval, embryo transfer, and the ensuing waiting period for results, are particularly stressful for women undergoing these procedures.[8,9] At the commencement of treatment, women often express significant concerns regarding the number of injections they must endure, the dietary limitations required for optimal results, the expected physical discomfort, and most importantly, the probability of achieving a successful IVF cycle. During subsequent monitoring appointments, their apprehension centers on the advancement of their treatment. On the days designated for oocyte retrieval and embryo transfer, women experience anxiety related to the quality and quantity of the eggs and embryos, respectively. Many women have identified the two-week waiting period following embryo transfer, during which they await pregnancy results, as the most stressful phase of the entire process.[10]

The distinction in anxiety and depression levels among infertile couples at various stages of IVF and their correlation with assisted pregnancy outcomes have not been frequently examined. Previous studies indicate that the effectiveness of IVF may be influenced by psychological factors, including the level of distress experienced by women prior to and during treatment, but other studies find no association. Therefore, this study investigates anxiety and depression faced by women at different stages of IVF and analyzes their association with pregnancy outcomes.

METHODS

This study was designed as an analytical cohort study to assess the impact of IVF on the psychiatric aspects of women undergoing the treatment, particularly the presence of anxiety and depression. Data collection was conducted at Yasmin Infertility Clinic, Cipto Mangunkusumo General Hospital (RSCM), and Dr Sander B. Daya Medika Clinic from May 2018 to March 2023. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (ND308/UN2.F1/ETIK/PPM0002/2023).

The calculated target sample size was 100 participants including drop out of 20%. Women aged 25-42 years scheduled for IVF were eligible for participation. Exclusion criteria included individuals with psychotic disorders, severe anxiety, and severe depression. Participants were selected using non-probability, consecutive sampling, enrolling each eligible woman until the target sample size was achieved. Screening for severe mental disorders was conducted using the Mini-International Neuropsychiatric Interview (M.I.N.I.) instrument, a semi-structured interview

to diagnose mental disorder based on the diagnostic criteria of International Classification of Disease (ICD)-10. Each woman gave written consent prior to participating in the study.[11]

Study data was collected using structured questionnaires at important time points throughout IVF; before the start of the treatment, before embryo transfer, and before pregnancy test. Demographic and gynecological information were obtained using questionnaires and the subjects' medical records at the initial stage of the study. Anxiety and depression symptoms, as the primary outcomes, were assessed using Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Depression Rating Scale (HAM-D). Both instruments consist of semi-structured interviews conducted by a trained psychiatrist.

HAM-A, which contains 14 items, assesses anxiety severity through components including anxious mood, tension, fears, insomnia, difficulty in concentrating, and physical symptoms related to anxiety. The scale was translated and validated for the Indonesian population, achieving a Cronbach's alpha reliability coefficient of 0.756.[12] HAM-D, which comprises 17 items, evaluates the severity of depression based on components such as mood, feelings of guilt, suicidal ideation, insomnia, work performance and activities, psychomotor retardation or agitation, anxiety, somatic symptoms, and weight loss. This scale has undergone translation and validation for the Indonesian population, exhibiting a sensitivity and specificity of 93.3%.[13] The semi-structured interviews were conducted by the same trained psychiatrist to ensure consistency in scoring. Scores greater than or equal to 8 HAM-A and HAM-D were used to classify mild to moderate anxiety and depression, respectively, based on thresholds validated in previous studies for the Indonesian population. Pregnancy results were obtained from the medical record, evaluating urinary beta-hCG results approximately six weeks after recruitment as a part of IVF's routine procedure.

The data obtained was then subjected to analysis utilizing Statistical Package for the Social Sciences (SPSS) version 27. Participants who dropped out were excluded from the analysis. Categorical variables were analyzed using Chi-Square and Fisher's exact tests as appropriate, to examine associations between demographic, gynecological, anxiety, depression, and pregnancy outcome variables. For longitudinal analysis of anxiety and depression scores across the IVF, the Friedman ANOVA test was applied, followed by post hoc analysis with Bonferroni adjustment.

RESULTS

Out of 100 samples initially planned, 87 subject data were ultimately collected. Thirteen subjects were excluded for not meeting the inclusion criteria. Throughout the study, 26 subjects dropped out at various measurement stages, with most dropouts related to the IVF procedure. A total of 61 subjects completed the study (Figure 1).

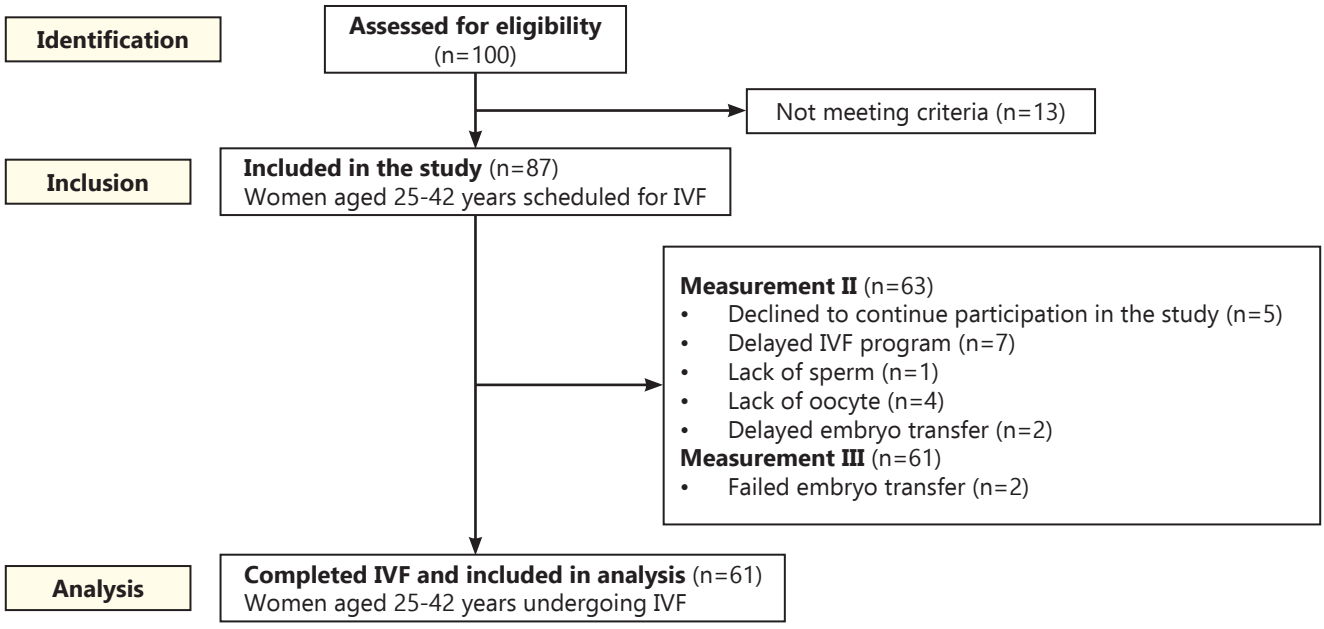

Figure 1. Flowchart of study design

Table 1 shows the distribution characteristics in research subjects at the initial stage of the study prior to the start of IVF. The majority of subjects was under 35 years (55.7%), having bachelor's or master's degree (90.2%), having been infertile for 5-10 years due to mixed etiology, planning to immediately have a child, and on their first cycle of IVF. At the beginning of the study, 42% of the subjects exhibited no anxiety or only minimal levels, while approximately 41% reported mild anxiety symptoms. Additionally, 52.5% of the participants experienced no depression or only minimal depressive symptoms.

Table 1. Subject Characteristics (n=61)

Characteristics	n	%
Demographic		
Age (y o)		
<35	34	55
35-37	17	27.9
38-40	8	13.1
>40	2	
Education level		
Bachelor's master	55	90.2
Associate's	6	9.8
Gynecological		
Duration of Infertility (years)		31
<5	19	50.8
5-10	31	18
>10	11	
Childbearing Plan		88
Not delaying	54	11.5
DElaying	7	
Type of Infertility Experienced		
Female	18	29.5
Male	10	16.4
Mixed	33	54.1
Psychiatric		
Anxiety		
Not present or minimum	26	42.6
Mid	25	41.0
Moderate	10	16.4
Depression		
Not present or minimum	32	52.5
Mild	27	44.3
Moderate	2	3.3

Figure 2 illustrates the changes in anxiety scores among research subjects based on the HAM-A instrument. There was an increase in anxiety scores observed in Measurement II, conducted before the embryo transfer phase, which then tended to stabilize in Measurement III, conducted prior to the beta- hCG examination. A slightly different pattern was observed in depression scores among research subjects based on the HAM-D instrument (Figure 3), which showed an increase in Measurement II and a further rise in Measurement III.

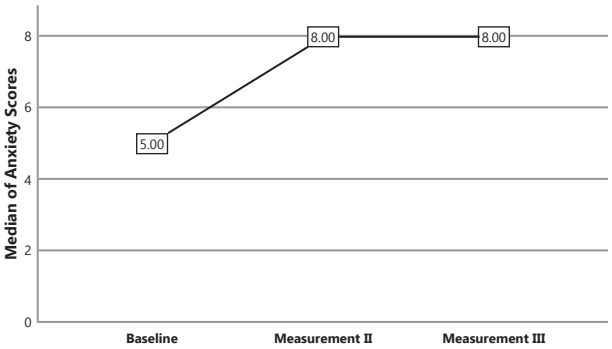

Figure 2. Anxiety Levels throughout IVF based on the Hamilton Anxiety Rating Scale (HAM-A)

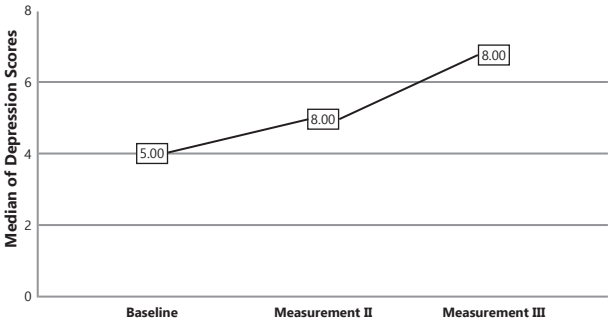

Figure 3. Depression Levels throughout IVF based on the Hamilton Depression Rating Scale (HAM-D)

The study revealed significant changes in anxiety and depression throughout IVF. Anxiety levels, as measured by the HAM-A scale, showed a significant rise across the IVF timeline ($p < 0.001$, Kendall's $w = 0.19$). The HAM-A scores rose markedly from a median of 5.00 (range: 0.00–18.00) at baseline to 8.00 (range: 0.00–20.00) before embryo transfer, maintaining this level until before the pregnancy test ($p < 0.001$). Similarly, depression levels, captured using the HAM-D scale increased from a median of 4.00 (range: 0.00–16.00) at baseline to 5.00 (range: 0.00–15.00) before embryo transfer and reaching 7.00 (range: 0.00–16.00) before the pregnancy test ($p = 0.001$, Kendall's $w = 0.121$).

Anxiety and depression scores showed a significant increase over time, as indicated by the Friedman ANOVA test. The median anxiety score rose from 5.00 at baseline to 8.00 at both Measurement II and III ($p < 0.001$), with a Kendall's W of 0.19, suggesting a moderate effect size. Similarly, depression scores increased from a median of 4.00 at baseline to 5.00 and 7.00 in subsequent measurements ($p = 0.001$), with a Kendall's W of 0.121, indicating a weaker but still meaningful trend.

These findings suggest a consistent upward shift in both anxiety and depression levels across the three time points, with statistically significant changes and modest agreement in rank ordering.

The analysis revealed significant changes in anxiety and depression scores over time. Anxiety scores showed a moderate correlation (r = 0.50) between baseline and both Measurement II and III, with highly significant p-values (< 0.001), indicating a notable increase in anxiety symptoms. However, no change was observed between Measurement II and III (r = 0.00, p = 1.00), suggesting a plateau in anxiety levels.

Similarly, depression scores increased significantly from baseline to Measurement II (r = 0.34, p = 0.026) and to Measurement III (r = 0.45, p = 0.001), reflecting a progressive rise in depressive symptoms. Yet, the difference between Measurement II and III was not significant (r = 0.11, p = 1.000), indicating stabilization in depression levels after the initial increase.

Post hoc analyses confirmed significant increases in both anxiety and depression during the course of IVF. It showed significant increases in anxiety levels from baseline to both before embryo transfer (r = 0.50, adjusted p < 0.001) and prior to the pregnancy test (r = 0.50, adjusted p < 0.001). The lack of a significant difference between the two latter measurements (p = 1.00) suggests sustained anxiety throughout the latter stages of the IVF process. This pattern highlights the potentially stress-inducing impact of certain important points during IVF and the necessity for targeted psychological support during these phases.

Post hoc analyses also revealed a statistically significant rise in depression levels from baseline to both subsequent measurements (r = 0.34, adjusted p = 0.026 and r = 0.45, adjusted p = 0.001, respectively). However, no significant difference was observed between scores before embryo transfer and before the pregnancy test (adjusted p = 1.00). This suggests a cumulative burden of emotional distress during the IVF cycle, potentially linked to hormonal influences, treatment expectations, and procedural stress.

Table 2. Association between Subject Characteristics and Anxiety Levels (n=61)

Characteristics		Anxiety								
		Baseline[a]		p	Measurement II[a]		p	Measurement III[a]		p
		No-Minimal Anxiety	Mild-Moderate Anxiety		No-Minimal Anxiety	Mild-Moderate Anxiety		No-Minimal Anxiety	Mild-Moderate Anxiety	
Demographic										
Age	< 35 years	25 (61.0%)	9 (45.0%)	0.238[C]	17 (63.0%)	17 (50.0%)	0.311[C]	14 (58.3%)	20 (54.1%)	0.742[C]
	≥ 35 years	16 (39.0%)	11 (55.0%)		10 (37.0%)	17 (50.0%)		10 (41.7%)	17 (45.9%)	
Education Level	Bachelor's or master's degree	37 (60.7%)	18 (29.5%)	1.000[F]	25 (41.0%)	30 (49.2%)	0.685[F]	23 (37.7%)	32 (52.5%)	0.388[F]
	Associate's degree	4 (6.6%)	2 (3.3%)		2 (3.3%)	4 (6.6%)		1 (1.6%)	5 (8.2%)	
Gynecological										
Duration of Infertility	< 5 years	14 (34.1%)	5 (25.0%)	0.586[F]	7 (25.9%)	12 (35.3%)	0.542[F]	8 (33.3%)	11 (29.7%)	0.691[F]
	5-10 years	21 (51.2%)	10 (50.0%)		16 (59.3%)	15 (44.1%)		13 (54.2%)	18 (48.6%)	
	>10 years	6 (14.6%)	5 (25.0%)		4 (14.8%)	7 (20.6%)		3 (12.5%)	8 (21.6%)	
Childbearing Plan	Not delaying	35 (85.4%)	19 (95.0%)	0.409[F]	21 (77.8%)	33 (97.1%)	0.037[F]	20 (83.3%)	34 (91.9%)	0.418[F]
	Delaying	6 (85.7%)	1 (5.0%)		6 (22.2%)	1 (2.9%)		4 (16.7%)	3 (8.1%)	
Type of Infertility	Female Infertility	14 (34.1%)	4 (20.0%)	0.512[C]	8 (29.6%)	10 (29.4%)	0.914[C]	9 (37.5%)	9 (24.3%)	0.292[C]
Experienced	Male Infertility	6 (14.6%)	4 (20.0%)		5 (18.5%)	5 (14.7%)		5 (20.8%)	5 (13.5%)	
	Mixed Infertility	21 (51.2%)	12 (60.0%)		14 (51.9%)	19 (55.9%)		10 (41.7%)	23 (62.2%)	

a = Count (percentage); C = Chi-Square test; F = Fisher's Exact Test; *p value < 0.05*

Table 3. Association between Subject Characteristics and Depression (n=61)

Characteristics		Depression								
		Baseline[a]		p	Measurement II[a]		p	Measurement III[a]		p
		No-Minimal Anxiety	Mild-Moderate Anxiety		No-Minimal Anxiety	Mild-Moderate Anxiety		No-Minimal Anxiety	Mild-Moderate Anxiety	
Demographic										
Age	< 35 years	29 (56.9%)	5 (50.0%)	0.738[F]	25 (56.8%)	9 (52.9%)	0.785[C]	21 (58.3%)	13 (52.0%)	0.624[C]
	≥ 35 years	22 (43.1%)	5 (50.0%)		19 (43.2%)	8 (47.1%)		15 (41.7%)	12 (48.0%)	
Education Level	Bachelor's or master's degree	46 (90.2%)	9 (90.0%)	1.000[F]	39 (88.6%)	16 (94.1%)	1.000[F]	35 (97.2%)	20 (80.0%)	0.038[F]
	Associate's degree	5 (9.8%)	1 (10.0%)		5 (11.4%)	1 (5.9%)		1 (2.8%)	5 (20.0%)	
Gynecological										
Duration of Infertility	<< 5 years	17 (33.3%)	2 (20.0%)	0.117[F]	14 (31.8%)	5 (29.4%)	0.977[C]	12 (33.3%)	7 (28.0%)	0.888[C]
	5-10 years	23 (45.1%)	8 (80.0%)		22 (50.0%)	9 (52.9%)		18 (50.0%)	13 (52.0%)	
	>10 years	11 (21.6%)	0 (0.0%)		8 (18.2%)	3 (17.6%)		6 (16.7%)	5 (20.0%)	
Childbearing Plan	Not delaying	44 (86.3%)	10 (100%)	0.587[F]	37 (84.1%)	17 (100.0%)	0.175[F]	30 (83.3%)	24 (96.0%)	0.223[F]
	Delaying	7 (13.7%)	0 (0.0%)		7 (15.9%)	0 (0.0%)		6 (16.7%)	1 (4.0%)	
Type of Infertility Experienced	Female Infertility	15 (29.4%)	3 (30.0%)	0.900[F]	13 (29.5%)	5 (29.4%)	0.206[C]	13 (36.1%)	5 (20.0%)	0.385[C]
	Male Infertility	8 (15.7%)	2 (20.0%)		5 (11.4%)	5 (29.4%)		5 (13.9%)	5 (20.0%)	
	Mixed Infertility	28 (54.9%)	5 (50.0%)		26 (59.1%)	7 (41.2%)		18 (50.0%)	15 (60%)	

a = Count (percentage); C = Chi-Square test; F = Fisher's Exact Test; **p value < 0.05*

The association between subject characteristics and anxiety (Table 2) and depression (Table 3) levels during IVF showed no statistically significant relationships across all measurements. Demographic factors such as age and education level were not significantly associated with anxiety or depression at baseline, second, or third measurements ($p > 0.05$ for all comparisons). Gynecological factors, including duration of infertility, childbearing plans, and type of infertility, similarly demonstrated no significant influence on anxiety or depression levels at any time point ($p > 0.05$).

The only notable finding was a marginal association between education level and depression at the third measurement, where women with higher education appeared less likely to report mild-to-moderate depression compared to those with lower education ($p = 0.038$). Another minor association was also found between childbearing plan and anxiety in the second measurement, showing that women who delay their pregnancy are less likely to be anxious ($p = 0.037$) However, this association was not consistently observed across earlier measurements. Overall, neither demographic nor gynecological characteristics emerged as consistent predictors of anxiety or depression levels in this cohort.

There were no statistically significant differences in psychiatric symptoms—specifically anxiety and depression—between pregnant and non-pregnant women across three measurement points. At baseline, mild to moderate anxiety was reported in 36.1% of pregnant women and 28.0% of non-pregnant women ($p = 0.507$), with similar patterns observed in subsequent measurements (p-values: 0.973 and 0.656). Depression levels followed a comparable trend, with mild to moderate symptoms increasing slightly over time but remaining statistically insignificant between groups (baseline $p = 0.727$; Measurement II $p = 0.985$; Measurement III $p = 0.896$).

Overall, both groups experienced fluctuations in anxiety and depression levels, yet the differences were not significant. This suggests that pregnancy status did not play a decisive role in influencing the severity of psychiatric symptoms within the observed sample.

These findings support earlier results showing that anxiety and depression symptoms increased over time during the IVF process, but were not influenced by pregnancy status or linked to pregnancy outcomes. Psychological distress appeared to rise regardless of clinical results, highlighting the need for emotional support throughout treatment.

DISCUSSION

Study, conducted at a tertiary hospital in Indonesia, is the first in the country to explore the impact of different stages of IVF on anxiety and depression levels in women undergoing

the treatment, as well as their relationship with pregnancy outcomes. The baseline characteristics observed in our sample largely align with those reported in other studies, supporting the generalizability of our findings. More than half of the research subjects were under 35 years old (55.7%), followed by those aged 35-37 years (27.9%), closely reflecting the demographic profile reported by the Indonesian Association for In Vitro Fertilization, which found that 50.07% of women undergoing IVF in Indonesia were under 35 years and 20.55% were aged 35-37 years.[14]

Furthermore, the majority of participants in our study had bachelor's or master's degree (90.2%), which aligns with the results of prior studies.[15] Mixed infertility was the most common type observed in subject, aligning with the Indonesian Association for In Vitro Fertilization report, which identified mixed infertility in 40.22% of cases, followed by female infertility at 30.1% and male infertility at 22.71%.14 However, a notable difference in infertility duration was observed, with the majority of participants experiencing infertility for five to ten years. In contrast, previous research reported a typical infertility duration that aligned with marriage lengths of 1.5 to 6.2 years.[16] This discrepancy may be partly attributed to the lack of IVF coverage under Indonesia's national health insurance, unlike in some developed countries. Cultural and socioeconomic influences may contribute significantly, as prior research has identified enduring myths, misinformation, and adverse perceptions regarding IVF within certain segments of the Indonesian population.[17] These barriers may delay couples' pursuit of IVF, leading them to consider alternative treatments or save for the procedure due to its substantial cost.

At the beginning of the study, participants were at minimal levels of anxiety and depression, aligning with the results of prior studies that indicated anxiety and depression rates of 13.5% and 9.4%, respectively, among infertile couples before IVF.[18] Other previous research has indicated that the majority of women participating in IVF reported experiencing predominantly mild levels of anxiety and depression.[19] Based on demographic and gynecological characteristics, we found that the incidence of anxiety in measurement II (before embryo transfer) is related to childbearing plan. We also found that the depression in measurement III (before pregnancy test) is related to education level, but this association was not consistently observed across earlier measurements.

Anxiety and Depression Levels throughout IVF

IVF is a final-line reproductive method for addressing infertility issues in couples. The high cost of IVF, the extensive stages involved, and the often-uncertain outcomes make the experience emotionally taxing, with many women describing the journey as an "emotional roller coaster." Women may experience symptoms of anxiety or depression that can impact their adaptability and the success of IVF.[20] In a previous study that involved 42000 women in Denmark, 35% were screened positive for depression before starting IVF.[21] Another study conducted in 5 fertility practices in California found depression in 56.5% and anxiety in 75.9% of the women seeking infertility treatment.[22]

The results of this study revealed significant changes in anxiety and depression throughout IVF. Anxiety levels, as measured by the HAM-A scale, showed a significant rise across the IVF timeline ($p < 0.001$, Kendall's $w = 0.19$). Depression levels, as measured by the HAM-D scale, also showed a significant rise across the IVF timeline ($p = 0.001$, Kendall's $w = 0.121$). This pattern is consistent with the findings of prior research, which indicated that anxiety levels in women undergoing IVF typically rise before and after embryo transfer (the period awaiting pregnancy test results), often attributed to heightened emotional responses during this time.[20] The incidence of depression is also noted to vary during the IVF process; however, it exhibits a slight distinction, as prior research has shown that peak levels of depression are typically observed immediately prior to the commencement of the IVF cycle.[19]

These findings are supported by post hoc analysis, which revealed significant increases in both anxiety and depression during IVF. The findings of this study are consistent with earlier research, which also identified a comparable trend in the fluctuations of anxiety and depression during the various phases of in vitro fertilization (IVF).[19] Prior to embryo transfer, women tend to harbor elevated expectations regarding the success of IVF and exhibit apprehension regarding the oocyte retrieval procedure, particularly when performed without general anesthesia, which can exacerbate fears of pain and induce anxiety. Following embryo transfer, patients express concerns related to

the investment of time and financial resources, the efficacy of their psychological efforts, and the potential implications of a failed outcome. A prior investigation similarly found that women undergoing IVF experience the highest levels of anxiety post-embryo transfer, corroborating the results of this study, which indicates a sustained state of anxiety from the period preceding embryo transfer until the pregnancy test is conducted.[23]

Association Between Anxiety, Depression and Pregnancy Outcomes

The results of this study indicate that there was no association between anxiety and depression scores and pregnancy outcomes across the three measurement points during IVF. Previous research has yielded comparable results, indicating a lack of correlation between anxiety and depression and the rates of clinical pregnancy.[24] A study conducted in China found no significant differences between anxiety levels in women who obtained pregnancy in IVF and those who did not.[25] A similar study also found no association between the IVF outcome and psychological distress of women who did not obtain clinical pregnancy after their first embryo transfer.[26]

The success of pregnancy through IVF can be attributed to a variety of factors, particularly those related to infertility. Conditions like obstructed fallopian tubes or male infertility can hinder the treatment process and diminish the likelihood of a successful outcome. Moreover, the quality of both oocytes and embryos, along with the thickness of the endometrium, plays a vital role in achieving successful fertilization and implantation. The presence of higher-quality oocytes and embryos markedly enhances the probability of conception. Additionally, numerous studies have underscored the significant impact of lifestyle choices on IVF success. Habits such as smoking, excessive alcohol intake, and obesity can adversely influence the effectiveness of IVF treatments.[27-30]

While anxiety and depression may not directly correlate with lower pregnancy rates, they can lead to diminished well-being after unsuccessful treatments. A prior investigation indicated an increase in both depression and anxiety in couples after IVF treatment failure.[31] Another study found that infertile women with high levels of depression and anxiety symptoms had a lower quality of life following unsuccessful IVF treatment.[32] Therefore, psychosocial intervention and support should be provided effectively to reduce the psychological distress in these women.

Strengths and Limitations of the Study

Key strengths of this study include long-term monitoring throughout the IVF, enabling a clear observation of the increasing levels of depression and anxiety at each stage. However, there were limitations, one of which was this study is a prospective cohort study aimed at examining the levels of anxiety and depression in women undergoing IVF, without comparing them to a group receiving other infertility treatments. Therefore, the results cannot be definitively attributed solely to IVF, as they may also be influenced by other factors. A further constraint is the challenge associated with recruiting participants for the study. This study faced a relatively high dropout rate, which may have influenced the statistical power and generalizability of the findings. The dropouts can be attributed to several factors inherent to IVF, which is a dynamic procedure, and some participants experienced unexpected outcomes during the treatment, which indicated IVF failure even before the final pregnancy results could be assessed. As a result, these women were unable to continue with the treatment, and hence, could not complete the study.

In addition, this study does not include an evaluation of biological factors that may impact the IVF process and ultimately pregnancy outcomes, such as quality of the sperm, oocyte, embryo, and differences in individual hormone levels. Thus, future research ought to explore the adoption of more flexible data collection method, develop strategies aimed at maintaining participant engagement throughout the IVF journey, and take into account confounding variables that could affect the outcomes of IVF treatments.

CONCLUSION

Our findings demonstrate a significant increase in anxiety and depression throughout the stages of IVF, particularly before embryo transfer and while waiting for pregnancy test results. The foremost determinant affecting anxiety in measurement II (prior to embryo transfer) is childbearing plan, whereas the most critical factor linked to depression in measurement

III (before the pregnancy test) is the degree of educational attainment. Nonetheless, this correlation was not uniformly evident across all measurements and should be approached with caution in interpretation. These findings have important implications for clinical practice, as they underscore the necessity of mental health screening for all women undergoing IVF. Additionally, providing psychiatric support for women experiencing anxiety and depression during IVF is crucial to ensure their comfort and enable them to navigate the treatment more effectively.

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CONFLICT of INTEREST

No competing interests were disclosed.

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Research Article

Vaginal Microbial Patterns and Matrix Metalloproteinase-9 Levels in relation to Premature Rupture of Membranes

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Abstract

Introduction: Premature rupture of membranes (PROM) is a significant cause of perinatal morbidity, with infection considered a primary etiological factor. The local interplay between vaginal microbiota and matrix metalloproteinase-9 (MMP-9), an enzyme crucial for fetal membrane degradation, is not fully understood. This study aimed to investigate the association between vaginal microbial patterns, local MMP-9 levels, and the incidence of PROM.

Methods: This cross-sectional study was conducted in Makassar, Indonesia, and included 60 pregnant women: 30 with PROM and 30 non-PROM controls. PROM diagnosis was established through clinical examination and confirmed using sterile speculum assessment, nitrazine pH test, and fern test. Vaginal swabs were collected for microbiological culture and bacterial identification. MMP-9 concentrations were quantified from the vaginal swab supernatants using an enzyme-linked immunosorbent assay (ELISA).

Results: The PROM group had a significantly higher prevalence of Gram-negative bacteria compared to the control group (83.3% vs. 56.7%, p=0.024), with *Escherichia coli* being the most predominant organism associated with PROM (p=0.004). Mean MMP-9 levels were significantly elevated in the PROM group compared to controls (1706.78 ng/mL vs. 1328.20 ng/mL, p=0.006). Furthermore, MMP-9 concentrations were significantly higher in women colonized by Gram-negative bacteria than those with Gram-positive flora (p=0.020).

Conclusion: High vaginal MMP-9 concentrations and the predominance of *E. coli* and other Gram-negative bacteria were strongly associated with PROM. These findings suggest that elevated vaginal MMP-9 may serve as a potential biomarker for PROM risk and reflect microbial-induced extracellular matrix degradation.

Keywords: Microbial Patterns, *Escherichia coli,* Premature Rupture of Membrane, Matrix Metalloproteinase 9, Vaginal microbiota.

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INTRODUCTION

Preterm rupture of membranes (PROM) is the rupture of the amniotic sac before the onset of labor.[1–3] PROM is characterized by painless discharge of fluid from the vagina. PROM can occur before and after 37 weeks of pregnancy. The prevalence of PROM worldwide varies between 5% and 15% of all gestations.[4] Globally, the incidence of preterm PROM varies between 13.7% in Ethiopia, 7.5% in Uganda, 5.3% in Egypt, and 1.4% in the USA.[5] In Makassar, a study reported that the incidence of PROM was 5.55%.[6]

PROM may precipitate fetal distress as a consequence of placental abruption or umbilical cord compression, intraventricular hemorrhage and sepsis; it may elevate the likelihood of cesarean delivery due to irregularities in fetal heart rhythm; respiratory distress syndrome; and adverse long-term neurodevelopmental consequences such as auditory or visual impairments, intellectual disabilities, motor and developmental delays, intrauterine fetal death or cerebral palsy. PROM also causes maternal infection (15%-25%),

placental abruption (9%-12%), chorioamnionitis (13%-60%), and increases the risk of disseminated intravascular coagulopathy.[4]

The etiology of PROM might occur due to bacterial infection where pathogenic bacteria trigger the immune response of the mother and fetus, resulting in changes in the uterine cavity that cause premature labor.[7] The colonization of the vaginal microbiota by pathogenic bacteria elicits an activation of the local immune response, which subsequently influences systemic immunity, thereby instigating an inflammatory cascade that ultimately culminates in the reorganization and disturbance of the membrane architecture and PROM.[8]

Other studies have reported that the pathophysiology of PROM due to infection occurs because of prostaglandins and matrix-degrading enzyme production through pro-inflammatory cytokines and microbial endotoxins released after the binding of organisms to ex-toll like receptors. This condition causes an increase in matrix metalloproteinase (MMP), which plays a role in collagen degradation and leads to a decrease in membrane tensile strength, resulting in membrane rupture.[9]

During labor (preterm or term), rupture of the membranes correlates with a marked elevation in the concentration of active matrix metalloproteinase-9 (MMP-9), alongside a notable reduction in the median levels of active tissue inhibitors of metalloproteinase (TIMP)-2 and TIMP-1.[10,11] Bacterial vaginosis, one of the common infections in women, in most studies can increase the levels of beta interleukin (IL)-1 in women, which leads to activation of MMPs such as MMP-1 and MMP-9.[12] Therefore, we conducted this study to analyze the microbial patterns and MMP level in the incidence of PROM, especially MMP-9.

MATERIALS AND METHODS

Study design

This observational study utilized a cross-sectional design and was conducted at St. Khadijah I Hospital in Makassar, Indonesia, from April 2024 to August 2024.

Study population and sample

A total of 74 pregnant women presenting to St. Khadijah I Hospital during the study period were screened for eligibility using a consecutive sampling method, in which all participants meeting the inclusion criteria were enrolled until the required sample size was achieved.

The sample size was determined using Lemeshow formula.[13–15] or two independent groups, with an expected proportion difference of 0.3, a confidence level of 95%, and statistical power of 80%. The minimum required sample size was 24 subjects per group, but to account for potential data loss, 30 participants were included in both the PROM and non-PROM groups.

The inclusion criteria for the PROM group were as follows: (1) confirmed diagnosis of premature rupture of membranes, defined as the spontaneous rupture of the amniotic membrane before the onset of labor with clinical evidence of fluid leakage from the vagina; (2) singleton pregnancy; (3) gestational age of ≥32 weeks confirmed by ultrasonography; and (4) willingness to provide written informed consent.

The exclusion criteria were: (1) history of antibiotic therapy within the previous two weeks, (2) evidence of systemic or genital infection during pregnancy (e.g., urinary tract infection, chorioamnionitis, or vaginitis), (3) multiple gestation, (4) preexisting chronic conditions such as diabetes mellitus or hypertension, and (5) history of preterm delivery or cervical cerclage.

Of the 74 participants screened, 14 were excluded (recent antibiotic use, n = 6; systemic/genital infection, n = 4; multiple pregnancy, n = 2; incomplete laboratory data, n = 2). The remaining 60 eligible participants were divided equally into the PROM group (n = 30) and non-PROM group (n = 30).

Diagnosis of PROM

The diagnosis of PROM was established based on a clinical history of painless leakage of clear amniotic fluid from the vagina prior to labor onset, confirmed by a sterile speculum examination revealing pooling of fluid in the posterior vaginal fornix. The diagnosis was further corroborated using two bedside tests: the Nitrazine (pH) test and the fern test. For the Nitrazine test, a sterile cotton swab was used to apply vaginal fluid to pH paper, with a color change to blue (pH≥6.5) considered positive. For the fern test, a vaginal fluid sample was smeared onto a glass slide, air-dried, and examined under a light microscope for a characteristic fern-like crystallization pattern. A definitive PROM diagnosis required positive

results from the clinical evaluation and both confirmatory tests.

Study procedure

After obtaining informed consent, all participants underwent a detailed clinical evaluation and vaginal swab collection in the hospital delivery room. Prior to sampling, the posterior vaginal fornix was cleansed using sterile gauze moistened with 0.9% NaCl solution. Vaginal swabs were obtained using Amies transport swabs (Copan, Italy) and stored at 2–8°C for a maximum of 24 hours before analysis.

Microbiological examination

Vaginal swab specimens were cultured on differential media, including MacConkey agar and blood agar, and incubated at 37°C for 24–48 hours. Bacterial colonies were identified based on Gram staining, colony morphology, and biochemical testing using the API 20E/20NE system (bioMérieux, France).

Measurement of MMP-9 levels

MMP-9 concentrations were quantified using the enzyme-linked immunosorbent assay (ELISA) method. Supernatant from each vaginal swab sample was centrifuged at 3000 rpm for 10 minutes to obtain a clear extract. The MMP-9 level was determined using a commercially available human MMP-9 ELISA kit (BT Lab, Catalog No. E0936Hu, Shanghai, China), following the manufacturer's protocol. Absorbance was read at 450 nm using a microplate spectrophotometer, and MMP-9 concentrations were calculated from a standard curve. All assays were performed in duplicate, and internal controls were included in each batch to ensure assay accuracy and reproducibility.

All laboratory analyses were conducted at the Hasanuddin University Medical Research Center. To ensure analytical reliability, each sample was processed in duplicate, and internal quality controls were included in each assay batch.

Data analysis

Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Univariate analysis calculated the percentages of patient characteristics and bacterial isolation results, as well as the mean and standard deviation of MMP-9 levels. Bivariate analysis examined relationships between two variables, with a normality test conducted using the Shapiro-Wilk test. If the data were normally distributed, an independent sample t-test was used; otherwise, the Mann-Whitney test was applied. For categorical data, a chi-square test was performed, and if its assumptions were not met, Fisher's exact test was used. All statistical tests were conducted at a 5% confidence level, with a p-value of <0.05 indicating significance.

Ethical clearance

The study was approved by the Human Biomedical Research Ethics Commission, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia under protocol number UH23070491.

RESULTS

A total of 74 pregnant women were enrolled in the study between April and August 2024. After screening, 14 participants were excluded due to recent antibiotic use (n = 6), urinary tract infection (n = 4), multiple pregnancy (n = 2), or incomplete laboratory data (n = 2). Consequently, the final analysis included 60 participants, who were divided equally into the PROM group (n = 30) and a non-PROM control group (n = 30), as outlined in the study flowchart (Figure 1).

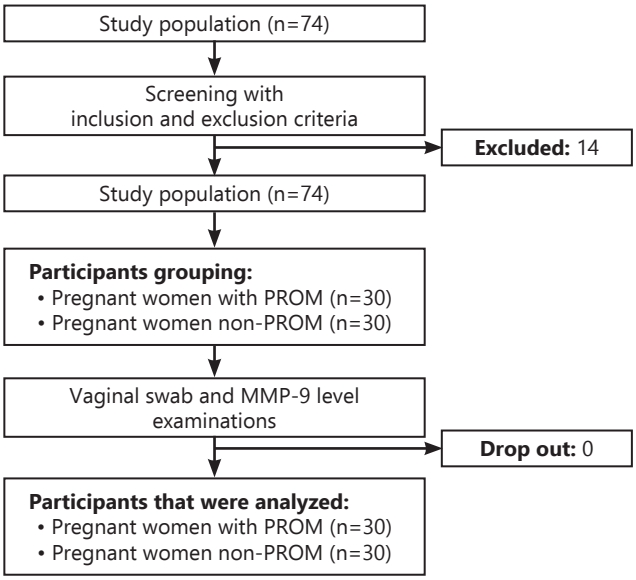

Figure 1. Flow Diagram of Study Participants. A schematic flowchart illustrates participant enrollment, exclusion, and final group allocation. Out of 74 eligible women, 14 were excluded due to ineligibility or incomplete data, leaving 60 subjects for final analysis (30 PROM, 30 non-PROM).

Participant Characteristics

Table 1 presents the demographic and obstetric characteristics of both groups. There were no significant differences between the PROM and non-PROM groups regarding age, body mass index (BMI), gestational age, parity, or educational level (p > 0.05 for all variables), indicating that both groups were comparable.

Table 1. Characteristics of study participants (n = 60)

Characteristics	PROM n (%)	Non-PROM n (%)	*P-value*
Age (years)			
< 20	3 (10.0)	1 (3.3)	
20-35	23 (76.7)	28 (93.3)	0.193
> 35	4 (13.3)	1 (3.3)	
BMI			
Underweight	2 (6.7)	1 (3.3)	
Normal	14 (46.7)	16 (53.3)	0.512
Overweight	9 (30.0)	5 (16.7)	
Obese	5 (16.7)	8 (26.7)	
Parity			
Nullipara	9 (3.0)	6 (20.0)	
Primipara	16 (53.3)	15 (50.0)	0.412
Multipara	5 (16.7)	9 (30.0)	
Gestational age			
Preterm (<37 weeks)	10 (33.3)	10 (33.3)	1.000
Aterm (≥37 weeks)	20 (66.7)	20 (66.7)	
Education (years)			
≤ 9	2 (6.7)	7 (23.3)	0.071
> 9	28 (93.3)	23 (76.7)	

Note: Data presented as frequency (percentage); p-values calculated using Chi-square or Fisher's exact test where appropriate; significance threshold set at p<0.05.

These findings confirm that the two groups were demographically comparable, minimizing potential confounding factors in subsequent analyses.

Microbial Patterns and PROM Incidence

Table 2 summarizes the distribution of vaginal microbial patterns. Eschericia coli (E. coli) was the predominant bacterium in the PROM group (72.0%) compared with the non-PROM group (28.0%), showing a significant association with PROM incidence (p = 0.004).

Similarly, the predominance of Gram-negative bacteria was significantly higher in the PROM group (83.3%) than in the non-PROM group (56.7%) (p = 0.024).

Table 2. Association between microbial patterns and incidence of PROM (n = 60)

Characteristics	PROM (n=30) n (%)	PROM (n=30) n (%)	*P-value*
Predominant bacteria			
E. coli	18 (72.0)	7 (28.0)	0.004*
Non-*E. coli*	12 (28.0)	23 (65.7)	
Microbial group			
Gram-positive	5 (16.7)	13 (43.3)	0.024*
Gram-negative	25 (83.3)	17 (56.7)	

*Note: Chi-square test applied; * indicates statistical significance (p<0.05).*

The predominance of Gram-negative bacteria, particularly E. coli, was significantly associated with the occurrence of PROM, suggesting a potential microbial role in membrane weakening.

MMP-9 Levels in Relation to Microbial Patterns and PROM

Table 3 presents the MMP-9 levels according to microbial patterns and PROM status.

The median MMP-9 concentration was significantly higher among samples dominated by Gram-negative bacteria compared to those with Gram-positive flora (1643.91 ng/mL vs. 1332.88 ng/mL; p = 0.020).

Similarly, MMP-9 levels were markedly elevated in the PROM group (1706.78 ± 386.36 ng/mL) compared to the non-PROM group (1328.20 ± 1556.22 ng/mL; p = 0.006).

Table 3. Relationship between MMP-9 levels, microbial patterns, and PROM incidence (n = 60)

Variable	Group	MMP-9 level (ng/mL) (Median [Min–Max] or Mean ± SD)	*P-value*
Microbial Pattern			
	Gram-positive (n = 18)	1332.88 [358.18–2255.89]	0.020*
	Gram-negative (n = 42)	1643.91 [658.18–2255.89]	
PROM Status	PROM (n = 30)	1706.78 ± 386.36	0.006*
	Non-PROM (n = 30)	1328.20 ± 1556.22	

*Note: Mann–Whitney test for microbial comparison; Independent samples t-test for PROM analysis; * indicates statistical significance (p<0.05).*

Higher MMP-9 levels were observed in women with PROM and in those colonized predominantly by Gram-negative bacteria. This suggests a synergistic interaction between microbial imbalance and extracellular matrix degradation in the pathogenesis of PROM.

DISCUSSION

This study demonstrated a significant association between vaginal microbial patterns, MMP-9 levels, and the incidence of PROM. Specifically, the predominance of *E. coli* and Gram-negative bacteria was strongly correlated with elevated MMP-9 concentrations in vaginal samples, suggesting a possible pathogenic mechanism involving microbial-induced extracellular matrix degradation.

Our findings align with previous studies reporting that bacterial infection contributes to PROM pathogenesis. Saghafi et al. (2018)[16] found that 68% of women with PROM had positive endocervical cultures, predominantly containing Gram-negative organisms, while Vanya et al. (2021) [17] and Abdelghany and Mounir (2018) [18] identified *E. coli* as the most common microorganism in PROM cases. The role of *E. coli* is biologically plausible, as its endotoxins mainly lipopolysaccharides (LPS) bind to Toll-like receptors (TLR-2, TLR-4, and TLR-9), activating downstream signaling cascades involving MyD88 and TRAF6. This cascade stimulates proinflammatory cytokines (IL-1β, IL-6, TNF-α) and induces MMP-9 expression, leading to degradation of collagen and weakening of the fetal membranes.[19,20]

Interestingly, *Staphylococcus aureus (S. aureus)* was also detected among PROM cases. Previous research has shown that S. aureus can promote thrombin formation through coagulase activity, triggering inflammation via protease-activated receptors (PARs) and compromising the structural integrity of the fetal membranes.[21] Although Gram-positive organisms were less prevalent in our study, their pathogenic potential remains relevant.

Our study differs from previous investigations in its methodological approach. Whereas prior studies primarily measured MMP-9 in amniotic fluid or serum, we quantified MMP-9 directly from vaginal swab samples—a less invasive yet reliable technique for detecting local biochemical changes associated with PROM. This methodological innovation may explain variations in absolute MMP-9 levels compared with other reports. Moreover, by simultaneously evaluating microbial profiles and MMP-9 concentrations, our study integrates infectious and biochemical pathways, providing a more comprehensive understanding of PROM etiology.

The biological mechanism underlying these associations involves infection-induced inflammation and matrix remodeling. Endotoxins and other bacterial components stimulate the production of prostaglandins and proteolytic enzymes, including MMPs, which collectively degrade the extracellular matrix (ECM) and reduce the tensile strength of fetal membranes.[11,22] Elevated MMP-9 levels, in particular, have been strongly linked to decreased collagen content and increased risk of membrane rupture.[23] Our results further support this relationship, as PROM cases showed significantly higher MMP-9 levels compared to non-PROM participants.

Regional microbial variation may also contribute to differing findings across studies. In Asian populations, *E. coli* and *Klebsiella* species are the predominant pathogens, whereas in Western countries, *Group B Streptococcus* is more common.[24] These differences likely reflect variations in vaginal microbiota composition, hygiene practices, and environmental conditions.

Notably, *E. coli* was also detected in 28% of non-PROM participants. This finding may reflect transient colonization or contamination, influenced by behavioral and environmental factors such as hygiene habits or sexual activity.[25,26] This underscores the importance of distinguishing between colonization and infection in assessing PROM risk.

To the best of our knowledge, this is one of the few studies to concurrently examine vaginal microbial profiles and MMP-9 levels in PROM using a minimally invasive approach. Our findings suggest that vaginal MMP-9 concentration may serve as a biomarker for early identification of women at risk for PROM, complementing existing diagnostic methods. By establishing a mechanistic link between microbial dysbiosis and ECM degradation, this study contributes to a more integrated understanding of PROM pathophysiology.

This study has several limitations. The relatively small sample size and single-center design may limit the generalizability of the findings. Additionally, we did not evaluate other metalloproteinases (e.g., MMP-2) or TIMPs, which could provide a broader view of matrix

remodeling. Behavioral factors such as hygiene and sexual practices were not controlled and may have influenced microbial composition. Future research should employ larger, multicenter designs and incorporate longitudinal sampling to confirm whether elevated vaginal MMP-9 levels precede membrane rupture. Advanced molecular techniques, such as next-generation sequencing, may also improve microbial characterization and predictive modeling.

CONCLUSION

The findings revealed that the predominance of *E. coli* and other Gram-negative bacteria was significantly associated with increased vaginal MMP-9 levels and the incidence of PROM. These results suggest that microbial imbalance may trigger an inflammatory cascade that elevates MMP-9 production, leading to extracellular matrix degradation and membrane rupture. The measurement of vaginal MMP-9 levels using a simple ELISA-based approach may serve as a potential biomarker for early identification of women at risk of PROM. Understanding the interplay between vaginal microbiota and MMP-9 expression provides valuable insight into the underlying pathophysiology of PROM and supports the need for preventive strategies, including microbial monitoring during pregnancy. Future studies should explore other MMP isoforms and their inhibitors, as well as broader microbial profiling using molecular techniques, to further elucidate the mechanisms linking infection, inflammation, and membrane integrity.

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Declarations of interest

None

AUTHOR CONTRIBUTIONS

All authors contributed substantially to the conception and design of the study, data collection, analysis, and manuscript preparation. TM (Conceptualization, study design, supervision, and final approval of the manuscript), MTC (Data collection, laboratory analysis, and interpretation of results), RBL (Literature review and drafting of the manuscript), FH (Statistical analysis critical revision of the manuscript, and formatting for journal submission), EW (Literature review and drafting of the manuscript), and SNA (Literature review and drafting of the manuscript). All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Research Article

Relationship of History of Hypertension with Severity and Onset of Preeclampsia: A Retrospective Cohort

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Abstract

Objective: This study aimed to find correlation between a history of hypertension with severity and onset of preeclampsia.

Methods: A retrospective cohort study with retrospective analysis of medical record data in patients with preeclampsia and severe preeclampsia from November 2021 – February 2022 was conducted at dr. Soediran Mangun Sumarso Regional General Public Hospital, Wonogiri, Central Java. Analysis was performed between the history of hypertension with severity and onset (<34 weeks and age ≥ 34 weeks gestational age). Data analysis was performed using SPSS software with univariate Chi-Square analysis.

Results: A total of 44 medical record data were obtained in this study. A total of 20 patients (45.5%) had a history of hypertension and 24 (55.5%) patients had no history of hypertension. A total of 23 patients (52.3%) were diagnosed with severe preeclampsia and 21 patients (47.7%) were diagnosed with preeclampsia. Based on statistical analysis, it was found that there was no significant correlation between the history of hypertension and the severity of preeclampsia (p=0.741; OR (CI 95%): 0,818 (0,249 – 2,690)) and onset (p=0.88; OR (CI 95%): 1,133 (0,222 – 5,788)).

Conclusion: There is no relationship between history of hypertension with the severity and onset of preeclampsia. Further studies with larger populations are needed to analyze the relationship between history of hypertension and preeclampsia.

Keywords: blood pressure, cardiovascular disease, hypertension, onset, preeclampsia.

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INTRODUCTION

The incidence of preeclampsia is increasing every year, with the incidence of preeclampsia according to the World Health Organization (WHO) being in the range of 2 -10% of pregnancies worldwide.[1] The incidence of preeclampsia in Indonesia is 128,273 per year or around 5.3%. Preeclampsia affects 5-7% of pregnancies, causing 500,000 neonatal deaths each year.[2] The incidence of preeclampsia in Indonesia reaches 25% of all causes of maternal and infant mortality.[3] Preeclampsia can develop from various risk factors such as individual factors (pregnancy history, age, family history of hypertension, diabetes, chronic kidney failure), socioeconomic and environmental factors (where the risk is higher in low socioeconomic groups, poor education), and environmental (exposure to air pollution and cadmium).[4–7] The rate of preeclampsia is greater in low- and middle-income countries due to the large disparity in maternal health outcomes with high-income countries.[8]

Preeclampsia is one of hypertension during pregnancy which is one of the most common pregnancy disorders. This is caused by the emergence of the risk of severe complications due to pregnancy disorders related to preeclampsia.[9] For maternal, preeclampsia can increase the risk of hypertension after childbirth, coronary heart disease, stroke, venous thromboembolism, and

other related-cardiovascular diseases risk.[10] In neonates, the condition of preeclampsia has the risk of inhibiting fetal growth and development due to impaired blood circulation resulting in low birth weight, premature birth, and other poor neonatal outcomes.[11] Hypertension during pregnancy is one of the main causes of maternal death worldwide, with preeclampsia being the second cause of maternal death in Indonesia.[3,12] Although several existing studies attempt to find preeclampsia therapy targets and improve maternal and perinatal health outcomes, however, Preeclampsia risk prevention screening is still an effective measure to reduce the risk of maternal and fetal death in countries with limited health resources..[13,14]

One of the main targets in antenatal care screening is a history of hypertension in pregnant women, either during or after pregnancy.[15] A history of hypertension is a risk factor for pregnancy disorders and can develop into gestational hypertension, resulting in poor maternal and perinatal outcomes.[2] A history of hypertension found during early pregnancy screening is an indicator of a high-risk pregnancy that requires close specialist observation.[16] Management of hypertension in pregnancy with adherence to therapy and regular monitoring of blood pressure is necessary to control blood pressure and reduce the risk of worsening the mother's condition.[2] Several studies have shown that untreated hypertension before pregnancy can also develop into preeclampsia.[17,18] However, few studies exist to assess the risk of a history of hypertension on the development of more severe preeclampsia and the onset of preeclampsia. This study aims to analyze the effect of a history of hypertension on preeclampsia patients with a risk of severity and onset of preeclampsia in a secondary hospital.

METHODS

The inclusion criteria in this study were medical record data and complete patient identity, patients diagnosed with preeclampsia and severe preeclampsia based on the definition based on the Indonesian Society of Obstetrics and Gynecology, which is "specific hypertension in pregnancy and other organ system disorders at gestational age above 20 weeks" and confirmed by a hospital obstetric specialist, registered patients who gave birth at dr. Soediran Mangun Sumarso Regional General Hospital, and inpatients. Exclusion criteria were incomplete medical records, patients diagnosed with eclampsia, and outpatients. Medical records that match the inclusion criteria then record their medical history to find out whether the patient has been diagnosed with hypertension. Analysis was performed between the history of hypertension with severity and onset (<34 weeks and age ≥ 34 weeks of gestation) of preeclampsia.

The sample size calculation was determined by the single population proportion formula based on the prevalence of preeclampsia from previous studies in previous study (14.54%)[19] with the prevalence of preeclampsia in Indonesia (5.3%), $\alpha = 0.05$ ($z = 1.96$), the margin of error 10%. The results obtained amounted to 19 - 47 samples needed.

The data obtained was then analyzed using the Statistical Product and Service Solution program version 21 statistical software. All data were analyzed using univariate Chi-Square test to analyzed correlation between history of hypertension with preeclampsia severity and onset. Categorical data is then arranged in percentage form, while numerical data is displayed in mean ± standard deviation form. P-value <0.05 was considered significant.

RESULT

Subject Characteristics

A total of 44 cases of pregnant women with preeclampsia were recorded in the medical record. The mean age of the patients was 30.84 ± 7.2 (17 – 44) years. The majority of the population is aged 20-35 years (68.2%). We found that the majority of pregnant women with preeclampsia had no history of hypertension (24 patients (54.5%)), were diagnosed with severe preeclampsia (23 patients (52.3%)), and more than half had a late-onset diagnosis (37 patients (84. 1%). The characteristics of our sample are shown in Table 1.

Table 1. Characteristic of Sample Study

Variables	Number (%)
Age (Mean ± SD)	30. 84 ± 7.2
≤ 19 year-old	2 (4.5)
20 – 35 year-old	30 (68.2)
≥ 36 year-old	12 (27.3)
Gestational age (weeks)	36.18 ± 4.2
Has history of hypertension	
Yes	20 (45.5)
No	24 (54.5)
Preeclampsia severity	
Preeclampsia	21 (47.7)
Severe preeclampsia	23 (52.3)
Onset	
Early-onset (<34 week)	7 (15.9)
Late-onset (≥ 34 weeks)	37 (84.1)

Of the 21 patients with preeclampsia, 9 of them had a history of hypertension, while 11 of the 23 patients with severe preeclampsia had a history of hypertension. Based on statistical analysis, we found no association (p > 0.05; OR (CI 95%): 0.818 (0.249 – 2.690)) between a history of hypertension and the severity of preeclampsia. The results of the statistical analysis are shown in Table 2.

Table 2. Statistical analysis between history of hypertension with preeclampsia severity.

Variables			Severity degree		OR (CI 95%)	*P-value*
			Preeclampsia	Severe Preeclampsia		
History of hypertenion	Yes		9	11	0.818 (0.249 – 2.690)	0.741
	No		12	12		
		Total	21	23		

Of the 44 patients, 37 of them were diagnosed with late-onset preeclampsia. A total of 17 of them had a history of hypertension. In 7 patients with early-onset preeclampsia, 3 patients had a history of hypertension. Based on statistical analysis, we found no association (p > 0.05; OR (CI 95%): 1,133 (0,222 – 5,788)) between a history of hypertension and the severity of preeclampsia. The results of the statistical analysis are shown in Table 3.

Table 3. Statistical analysis between history of hypertension with preeclampsia onset

Variables			Preeclampsia onset		OR (CI 95%)	*P-value*
			Early-onset	Late-onset		
History of hypertenion	Yes		3	17	1.133 (0.222 – 5.788)	0.88
	No		4	20		
		Total	7	37		

DISCUSSION

Based on our study, there is no relationship between history of hypertension in preeclampsia patients and the severity of the outcome and the onset of preeclampsia. Based on statistical analysis, it was found that there was no significant correlation between the history of hypertension and the severity of preeclampsia (p=0.741; OR (CI 95%): 0,818 (0,249 – 2,690)) and onset (p=0.88; OR (CI 95%): 1,133 (0,222 – 5,788)). The majority (more than 80%) of preeclampsia patients in our study period were diagnosed with late-onset preeclampsia. We found similar findings in a higher percentage of late-onset cases in the population-based study by You et al (2018).[20] However, our population proportions differ from the study by Verbeek et al in which the majority of the sample was diagnosed with early-onset preeclampsia.[21] Findings of late-onset preeclampsia are more common than early-onset and account for the majority of preeclampsia cases with a higher maternal death case in the early-onsets.[22,23]

Several existing studies have shown different results regarding the relationship between a history of hypertension during pregnancy and the onset of preeclampsia. Our results are similar to the studies of Serra et al (2020) and Wadhwani et al (2020) which showed no significant difference between chronic hypertension and the onset of preeclampsia[24,25], but our results differ from the

findings of Veerbek et al (2015) and Huang et al (2021) which show that hypertension has an influence on the onset of preeclampsia.[21,26] Early blood pressure checks in early pregnancy have been recommended by various guidelines for screening for the prevention of hypertension, whether it is gestational hypertension, superimposed preeclampsia, or preeclampsia.[27] Results from previous studies show although our findings show no association between a history of hypertension and onset, blood pressure checks during pregnancy are necessary for both healthy pregnancies and high-risk pregnancies.[28]

Our other findings show that there is no relationship between the history of hypertension and the severity of preeclampsia, which is different from the findings of another study by Nzelu et al (2018) which showed a history of hypertension in previous pregnancies can develop severe hypertension, preterm preeclampsia, and small-for-gestational age (SGA).[29] Maternal hypertension, either before or after previous pregnancy, increases the risk of stroke and cardiovascular mortality.[27] In addition, hypertension that occurs during pregnancy results in poor perinatal outcomes such as SGA and preterm birth.[30] Although various guidelines suggest a target for reducing blood pressure during pregnancy in cases of gestational hypertension, systolic blood pressure tends to increase between 31 – 47 mmHg and 31 mmHg in diastolic blood pressure in the third trimester of pregnancy.[31] This condition allows the development of pregnancy complications due to blood pressure which tends to increase which reflects vascular resistance.[31]

The unclear findings between hypertension and preeclampsia may be due to the overlapping pathophysiology of the development of hypertension into preeclampsia.[32] Hypertension that develops chronically before pregnancy produces various biomarkers such as pro-inflammatory cytokines (IL-6 and TNF–α) which can damage vascular endothelial cells and cell adhesion molecules which increase the risk of endothelial dysfunction.[33] In addition, oxidative stress due hypertension condition can reduce nitric oxide (NO) and vascular endothelial growth factor (VEGF) function in the process of vasodilation.[34] In cases of late-onset preeclampsia, blood vessels experience decompression which can cause the failure of important organs such as the heart, brain, and kidneys.[10] Hypertensive conditions can develop endothelial dysfunction due to oxidative stress, which also occurs in preeclampsia.[35] These findings can make the target of hypertension therapy and hypertension-related disorders of pregnancy and reduce the risk of complications of maternal hypertension.[32]

A study by Guy et al (2020) showed that early detection in the first trimester, including administration of antihypertensive drugs early in pregnancy to control hypertension, has the effect of preventing increases in blood pressure during pregnancy and reducing the use of more antihypertensive drugs.[36] However, this approach is not effective as a predictive tool for preeclampsia, even this is useful in clinical settings.[37] In addition, early detection of hypertension in pregnancy before it develops into preeclampsia is important to determine the referrals needed for pregnant women for birth planning by maximizing the referral system properly and effectively and reducing the burden on the national healthcare system.[38] Further studies in larger populations in different clinical settings are needed to make the risk assessment of preeclampsia from a history of hypertension more effective in determining the progression of preeclampsia.

Nevertheless, this study still has some limitations. The small study sample size was due to the limited duration and one study center in our data collection. We also did not compare our population with a healthy population, so we could not analyze the risk of developing preeclampsia in a healthy maternal (normotensive, without a history of hypertension) population. We also not recorded the degree of hypertension and previous hypertension treatment, so that this might be a confounding factor that influences the development of preeclampsia. Further research is needed in a wider and more diverse population in the future to assess the relationship between hypertension and the severity and onset of preeclampsia to improve the quality of maternal care and postnatal perinatal outcomes.

CONCLUSIONS

The relationship between the history of hypertension and the severity and onset of preeclampsia were can't be conclude in this study. This study population shows that more pregnant women who do not have a history of hypertension can experience preeclampsia, where many preeclampsia occur in late-onset of pregnancy. Routine blood pressure screening

before pregnancy is useful for early detection of the risk of preeclampsia and better pregnancy planning to reduce the risk of maternal mortality.

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Research Article

Effect of Bengkoang *(Pachyrhizus erosus)* Extract on Estrogen Receptor-β, Progesterone Receptor Expression, and Follicle-Stimulating Hormone Levels

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Abstract

Objective: Progesterone functions by inhibiting the release of Gonadotropin-Releasing Hormone (GnRH), which decreases Follicle-Stimulating Hormone (FSH) levels and converts them into hypoestrogens. This condition affects the expression of steroid, estrogen, and progesterone receptors, contributing to endometrial proliferation and secretion during the menstrual cycle.

Methods: This study aims to demonstrate that Bengkoang extract administration increases the expression of Estrogen Receptor (ER), Progesterone Receptor (PR), and Follicle-Stimulating Hormone (FSH) in Wistar model rats. This study divided 25 female Wistar rats into five groups: one control group without progesterone and Bengkoang extract and four treatment groups injected with progesterone. After exposure, Bengkoang extract was administered to three treatment groups at doses of 70 mg/200 g BW/day (treatment 1), 140 mg/200 g BW/day (treatment 2), and 280 mg/200 g BW/day (treatment 3).

Results: The results showed an increase in the expression of Estrogen Receptor- β (Erβ), Progesterone Receptor (PR), and Follicle-Stimulating Hormone (FSH) levels in treatment 1, treatment 2, and treatment 3 groups compared to the KP with $p < 0.05$

Conclusion: The study investigating the effect of Bengkoang (Pachyrhizus erosus) extract on estrogen receptor-β (ERβ), progesterone receptor (PR) expression, and follicle-stimulating hormone (FSH) levels has demonstrated significant findings.

Keywords: Estrogen, Estrogen receptor-β, Follicle-stimulating hormone, Pachyrhizus erosus, Progesterone, Progesterone receptor.

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INTRODUCTION

Hormonal balance plays a critical role in maintaining women's reproductive health and overall well-being[1]. Estrogen, progesterone, and follicle-stimulating hormone (FSH) are key regulators of the female reproductive system, influencing processes such as the menstrual cycle, fertility, and menopause[2,3]. Disruptions in the levels or activity of these hormones can lead to various reproductive disorders, including polycystic ovary syndrome (PCOS), infertility, and menopausal symptoms[3,4]. Estrogen receptor-β (ERβ) and progesterone receptor (PR) are essential components in the signaling pathways of these hormones, and their regulation is crucial for maintaining hormonal homeostasis[5,6].

Conventional hormone replacement therapies (HRT) are commonly used to manage symptoms of hormonal imbalances, particularly in menopausal women7. However, long-term use of synthetic hormones is often associated with an increased risk of side effects, such as cardiovascular diseases and certain types of cancers[5–7]. As a result, there has been growing interest in exploring safer, plant-based alternatives that could regulate hormone levels without adverse effects. Phytoestrogens, naturally occurring compounds in plants that mimic estrogen activity, have emerged as promising candidates for addressing hormonal imbalances. Among these, Bengkoang (Pachyrhizus erosus), also known as jicama, has gained attention due to its phytoestrogenic properties and traditional use in herbal medicine[3,8,9].

Bengkoang contains isoflavones, a class of phytoestrogens, which may exert estrogen-like effects by binding to estrogen receptors, particularly ERβ. This suggests that Bengkoang extract could potentially modulate estrogen and progesterone receptor activity, thereby influencing hormonal regulation. However, the effects of Bengkoang extract on specific hormone receptors and FSH levels have not been extensively studied. Understanding the impact of Bengkoang on ERβ, PR expression, and FSH levels could provide insights into its potential as a natural alternative for managing hormonal imbalances and improving women's reproductive health[5,6,10–12].

While Bengkoang is traditionally used for various health benefits, including skin care and anti-inflammatory effects, its potential role in modulating hormone receptors and balancing reproductive hormones remains poorly understood[12]. In particular, the specific effects of Bengkoang extract on estrogen receptor-β, progesterone receptor expression, and follicle-stimulating hormone (FSH) levels need to be explored[5,6]. This study aims to address this gap by investigating whether Bengkoang extract can influence these hormonal pathways, which are critical for maintaining reproductive health and managing conditions related to hormone imbalances. This study seeks to investigate the effect of Bengkoang (Pachyrhizus erosus) extract on the expression of estrogen receptor-β (ERβ), progesterone receptor (PR), and follicle-stimulating hormone (FSH) levels, aiming to evaluate its potential as a natural therapeutic agent for regulating hormonal balance in women. By elucidating the hormonal effects of Bengkoang extract, this research will contribute to the growing body of knowledge on plant-based alternatives for hormone regulation, with potential applications in treating conditions such as menopause, infertility, and hormonal disorders[2,3,8,10].

METHODS

The research was carried out at the Brawijaya University Institute of Biosciences laboratory, the pathology and anatomy laboratory, and the central biomedical laboratory at the medical faculty of Brawijaya University. This was a true experimental study with a post-test-only control group design in vivo. This research was conducted for 3 months and data analysis was conducted using the SPSS for windows 24 application. All procedures performed in studies followed the ethical standards of the Health Research Ethics Commission, Faculty of Medicine, Brawijaya University, with number 52/EC/KEPK-S2/02/2019, registered 12 February 2019-retrospectively registered, https://bit.ly/ethicalclearancesuryanti.

Material Animal attempt

The experimental animal was a white mouse strain of Wistar. As many as 25 animals, aged 8 to 10 weeks and weighing 160 to 225 grams, were sampled. The negative control (without progesterone and bengkoang extract exposure), the positive control (progesterone exposure without bengkoang extract), treatment 1 (progesterone exposure and bengkoang extract 70 mg/200grBW /day), treatment

2 (progesterone exposure and bengkoang extract 140 mg/200grBW/day), and treatment 3 (Bengkoang extract 280 mg/ 200grBW/day).

Bengkoang was obtained from the Kediri Regency in East Java. Bengkoang was dried and extracted at UPT Materia medica Batu integrated service unit , East Java, using a maceration method with 96% ethanol as the solvent.

Procedure

Each treatment group received four injections of progesterone hormone at a dose of 2.75 mg. Various doses of ethanol extract were administered orally to groups 1, 2, and 3 for 14 days using the sonde technique. After administering the extract, the rat's proestrus phase is surgically removed to extract the endometrium and blood from the heart. Immunohistochemistry was used to examine ERβ and PR expression in the endometrium, while ELISA measured FSH levels in the blood. ERβ and PR expression were observed in epithelial cells and endometrial stroma with ERβ and PR antibodies from Santacruz that were appropriate for Rattus norvegicus. The results were then observed using an Olympus dot slide with 400x magnification in 5 fields of view. ELISA kits for follicle-stimulating hormone (FSH) species of Rattus norvegicus were used to determine FSH levels.

Data evaluation

Data normality test using Shapiro-Wilk. Hypothesis testing using One-way ANOVA. Suppose Duncan's test follows significant differences (significant).

RESULT

The effect of bengkoang extract administration on the expression of Erβ and PR

The results of endometrial staining with hematoxylin-eosin were seen using an Olympus microscope with a magnification of 400 times. The calculation is done using five visual fields in each sample, then counting the number of glandular epithelium and the surface, and the results are averaged. The sample description can be seen as follows in Figure 1.

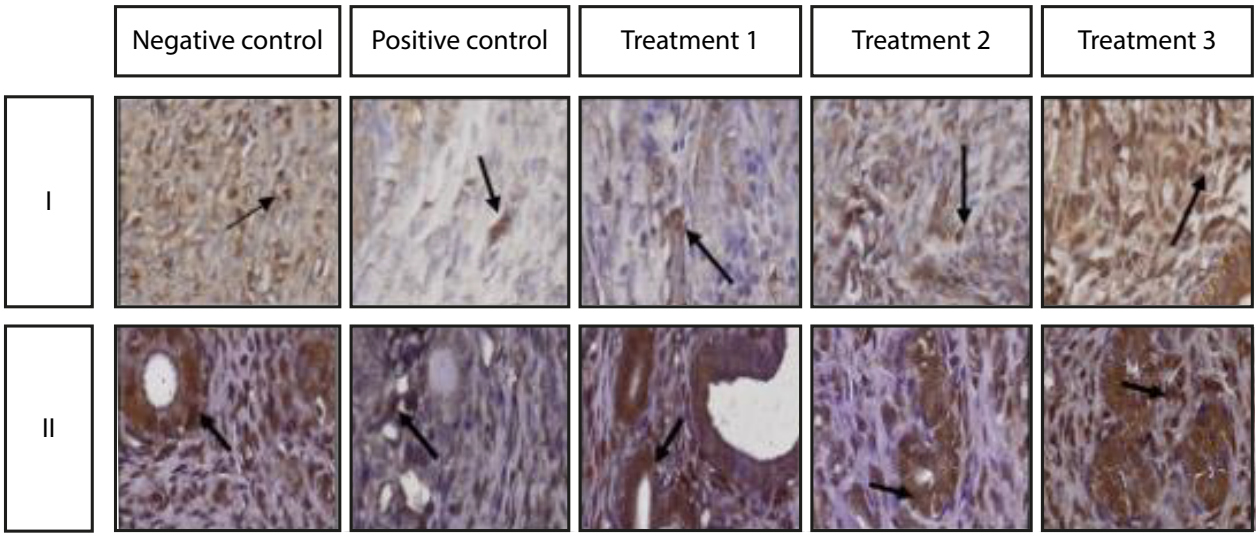

Figure 1. Overview of Erβ(I) and PR(II) expression in rat endometrium (400 times magnification)

Figure 1 depicts Immunohistochemical examination of the rat endometrium to observe the expression of Erβ and PR was indicated by cells appearing brown in color in the cell nuclei and membranes of the rat endometrium. Black arrows indicated the cells expressing ERβ and PR in the negative control group (without DMPA and Bengkoang extract), positive control group (DMPA without Bengkoang extract), treatment 1 group (DMPA with Bengkoang extract at 70mg/200gBW), treatment 2 group (DMPA with Bengkoang extract at 140mg/200gBW), and treatment 3 group (DMPA with Bengkoang extract at 280mg/200gBW). There was a noticeable difference in ERβ and PR expression between the negative control, positive control, treatment 1,2, and 3 groups. The expression of ERβ in each group appeared to vary, with the brown staining

being more prominent in the treatment 3 group compared to the others. The cells expressing ERβ in each image showed differences in the intensity of the brown color, with the treatment 3 group exhibiting the most brown staining, while the positive control group had the least. The brown staining was observed in both the epithelial and stromal compartments of the endometrium with more dominant staining in the stromal endometrium in the treatment 3 group. PR expression (II) results of immunohistochemical observations show that in the positive control group the expression of progesterone receptors is less than in the negative control group which is shown by brown discoloration with DAB staining. Whereas in groups treatment 1, treatment 2, and treatment 3 showed the results of changes in the number of expression of progesterone receptors in the endometrium after administration of ethanol extracts of Bengkoang with 3 different doses.

Table 1. Erβ, PR Expression and FSH Levels

	Erβ Expression (n=25)	PR Expression (n=25)	FSH (n=25)
Negative Control	19.02+3.36^{c}	68.176+6.5^{c}	182.75+19.49^{a}
Positive Control	5.62+1.23^{a}	43.988+8.1^{a}	47.59+7.89^{b}
Treatment 1	8.78+1.12^{ac}	50.936+5.1^{ab}	66.26+7.82^{c}
Treatment 2	15.2+1.87^{bc}	56.488+6.1^{b}	80.47+8.16^{d}
Treatment 3	39.9+11.48^{d}	66.98+3.8^{c}	102.96+12.05^{e}

Note: On the mean ± SD if loading different letters mean that there are significant differences (p-value <0.05) and if loading the same letters means there are no significant differences (p-value> 0.05).

Table 1 depicts the mean ER-β and PR expression in three groups of Rattus norvegicus female rats given DMPA and extracts. Bengkoang at 70 mg/200 grBW 140 mg/200 grBW and 280 mg/200 grBW. The image demonstrates that the highest average expression level of ER- β was seen in the treatment 3 group, meanwhile the lowest was seen in the positive control group This indicates that DMPA treatment promotes ER- β expression in female rats. The mean expression of ER- β appeared to be higher in the treatment 1, treatment 2, and treatment 3 groups than the positive control group; the expression of ER-β rose as the dose of Bengkoang extract was increased. Therefore, treatment of three doses of Bengkoang extract increases the expression of ER- in female Rattus norvegicus rats treated with DMPA. In contrast, the Bengkoang extract dose believed to boost ER- β expression the quickest is 280 mg/200 grBB, as the ER-β group in treatment 3 had the highest mean expression (39.9+11.48) compared to treatments 1 and 2. Compared to the positive control group with the lowest mean value, the PR expression increased in the treatment 1, treatment 2, and treatment 3 groups. The highest mean PR expression was found in KN, a condition typical of rats not administered DMPA injections and Bengkoang extract therapy. The expression of PR increases as the dose of Bengkoang extract is increased. Nonetheless, treatment 3 at a dose of 280 mg/200 gBW/day with an average value of 66.98 and the same homogeneity as evidenced by letter C on the average value is deemed to increase PR the most swiftly near standard conditions (negative control).

Effect of Bengkoang extract administration on FSH levels

Table 1 shows the average of FSH levels in rats that were not exposed to DMPA (negative control), rats that were exposed to DMPA (positive control), and three groups of hypoestrogenic rats administered Bengkoang ethanol extract at doses of 70 mg/200 g BW, 140 mg/200 g BW, and 280 mg/200 g BW. The fastest-acting dose of Bengkoang extract is 280 mg/200 g BW since the average FSH levels in the treatment 3 group (102.96 12.05 ng/mL) are closest to the intermediate FSH level in the negative control group (182.75 + 19.4 ng/mL).

DISCUSSION

Effect of Bengkoang extract administration on ER-β expression

ER-β is closely related to ER-α, and the positions of these estrogen receptors can complement one another [13]. ER-α is believed to

prevent estrogen-mediated actions mediated by ER-α [14]. ER-β has the opposite movement on the same gene promoter as ER-α in response to estrogen's effects [15]. Ovariectomized rats exhibit a distorted hyperproliferation response without estrogen and progesterone, but their adrenals produce relatively high levels of androgens. Androgens regulate ER-β via hydrogen receptors (AR) and inhibit breast cancer cell proliferation [16]. If a similar mechanism exists in the endometrium, androgens with high ER-β expression may inhibit excessive cell proliferation. Increased expression of ER-β in stromal cells is observed during the proliferative phase, with the color index halving during the secretory phase and remaining low during pregnancy [6,16].

Bengkoang is a plant that contains daidzein, phytoestrogens, and genistein, all of which can reduce cardiovascular risk and menopause-related symptoms [17,18]. Hypoestrogenic conditions in progesterone hormone users can reduce estrogen receptor expression and cause menopausal-like conditions[19]. As phytoestrogens in Bengkoang can bind to ER and stimulate cell proliferation, administering Bengkoang extract at the appropriate dose can enhance the effects of DMPA. Bengkoang phytoestrogens have an identical chemical structure to estrogen. Phytoestrogens can bind to estrogen receptors, particularly ER-β. His in vitro study on MCF-7 cells found that phytoestrogen content has differential and potent transactivation of ER-α and ER-β induced transcription, with ER-β activation 100 times stronger [17,20].

According to additional studies, genistein has no effect on the expression of ER-α mRNA in cultured pig granulosa cells. Aside from that, ER-β concentrations are higher in genistein-cultured cells than in control cells, and even higher genistein doses tend to increase ER-β in examined cells. Using IHC, ER-β is detected in the nucleus of granulosa cells, whereas ER-α is not detected [13]. In general, derivatives induce transcription-dependent receptors and are significantly more influenced by ER-β than ER-α. The concentration of genistein required to induce transcription is 104 times that of 17-beta estradiol. Considerably higher concentrations are necessary to stimulate cell growth.

All types of endometrial cells express ER-β, including canary epithelium and stromal cells. ER-β may be essential for the maintenance of the endometrial lining in rats. In contrast, ER-β mRNA expression throughout the menstrual phase is significantly lower than ER-α, despite ER protein expression being elevated throughout the menstrual cycle [14]. ER-β expression in the epithelium is linked to the menstrual cycle, which can increase estrogen levels and ER expression. This is due to the action of estrogen via ER-α and progesterone via PR, which has been demonstrated to increase ER-β transcription [15,16]. Therefore, the ER-β mechanism is the primary safety mechanism by which estrogen's intense mitogenic action can be limited to normal endometrium.

The influence of Bengkoang extract on the expression of PR

DMPA's interaction with progesterone receptors is also mediated by prostaglandin. Progesterone receptors A (PRA) also inhibits estrogen receptor activity (ER). Progesterone receptor A (PRA) and Progesterone Receptore B (PRB) are crucial for reproductive and non-reproductive activities in women. During the estrous cycle in rats or the menstrual cycle in women, estrogen and progesterone control the expression of progesterone receptors on epithelial cells, stroma, and uterine myometrial compartments[21]. High levels of synthetic progesterone that persist after DMPA administration reduce the amount of endogenous estrogen in the body by regulating the synthesis of progesterone receptors; PRA and PRB also decrease.

In this study, an immunohistochemical examination revealed that the expression of progesterone receptors was more significant in rats treated with varying doses of Bengkoang ethanol extract than in the positive control groups without medication. The results of the One-Way ANOVA test also demonstrate the effect of Bengkoang extract ethanol extract on groups receiving treatments 1, 2, and 3. In addition, Duncan's test revealed a statistically significant difference between the positive control and treatment groups. However, 280 mg / 200 gBW / day is considered the optimal dose based on the trend of the average amount to increase the expression of progesterone receptors as in normal conditions in the treatment group[22]. Due to changes in estrogen and progesterone receptors, endometrial bleeding and amenorrhea are influenced by a state of low estrogen and high progesterone during DMPA use [16].

Bengkoang extract contains phytoestrogens

called genistein, which regulate the expression of estrogen and progesterone receptors. [23]The phytoestrogens found in pumpkin seeds can increase estradiol production by decreasing ER--β and PR[24]. The administration of phytoestrogen-containing Bengkoang ethanol extract can increase the expression of progesterone receptors by increasing estradiol and regulating estrogen and progesterone receptors, as demonstrated by this study[25].

Impact of Bengkoang Extract on FSH Concentrations

High progesterone levels will stimulate neurons in the central nervous system to release opioid, dopaminergic, and gabaergic neurotransmitters, thereby inhibiting the release of GnRH. Low GnRH secretion stimulates the anterior pituitary to release low levels of FSH and LH. Low levels of FSH inhibit follicular development and maturation, thereby preventing ovulation [4,26]. Users of DMPA have FSH levels comparable to the early follicular phase. This state is maintained as a contraceptive effect of DMPA to prevent the development of follicles and ovulation [27,28]. The level of FSH in a Depomedroxiprogesterone-Acetat (DMPA) is equivalent to that of the luteal phase. This indicates that FSH levels are low during the luteal phase[28].

The research found that Bengkoang contains isoflavones with estrogen-like chemical structures [8]. Isoflavones have a chemical structure similar to 17-estradiol and possess estrogen-like properties. Bengkoang isoflavones (daidzein and genistein) have a system and estrogen-like activity identical to 17-estradiol. Thus, Bengkoang can be concluded to be a natural estrogen source[11].

They have demonstrated that consuming isoflavone-containing foods (genistein and daidzein) can affect ovarian function [29]. This is because ovarian function is regulated by hormones circulating throughout the body. Estrogen is the primary hormone responsible for the female reproductive cycle. Estrogen is primarily produced in the ovaries, enters the bloodstream, and sends a response signal to the brain. The hypothalamus and anterior pituitary are the brain regions responsible for regulating reproductive hormones. Estrogen stimulates the hypothalamus to generate GnRH, which then signals the anterior pituitary to generate FSH and LH. The hormone enters the bloodstream and signals the ovaries to produce an egg. Compounds with estrogenic activity can influence this signaling and elicit a response. When consumed, food containing estrogenic compounds (phytoestrogens) can bind to estrogen receptors. The hypothalamus and pituitary gland produce the ovulation-regulating gonadotropins FSH and LH in response to estrogen. Estrogen signaling in the ovary regulates gene expression required for follicular development and presentation of FSH and LH receptors, which respond to gonadotropin signals from the hypothalamus and pituitary[2]. In addition, phytoestrogens reduce the formation and activity of free radicals in the hypothalamus, preventing a decrease in hormone secretion [30,31].

CONCLUSIONS

The study investigating the effect of Bengkoang (Pachyrhizus erosus) extract on estrogen receptor-β (ERβ), progesterone receptor (PR) expression, and follicle-stimulating hormone (FSH) levels has demonstrated significant findings. Bengkoang extract, particularly at higher doses, was found to modulate hormone receptor activity and hormone levels in a dose-dependent manner.

1. ERβ Expression: The immunohistochemical analysis revealed a marked increase in ERβ expression in the endometrium, particularly in the P3 group (DMPA with Bengkoang extract at 280 mg/200gBW), as evidenced by the greater intensity of brown staining compared to other groups. This suggests that Bengkoang extract may enhance estrogenic activity by increasing ERβ expression, indicating its potential as a phytoestrogenic agent.
2. Progesterone Receptor Expression: Bengkoang extract also showed an effect on progesterone receptor expression. Higher doses of the extract, particularly in the P3 group, may have contributed to a regulatory effect on PR, aligning with the extract's potential role in balancing estrogen and progesterone signaling pathways.
3. FSH Levels: The study indicated that Bengkoang extract influenced FSH levels, suggesting that the extract may contribute to the modulation of pituitary-gonadal axis activity. The changes in FSH levels observed in the treatment groups point toward the extract's ability to affect overall hormonal regulation.

In conclusion, Bengkoang extract exhibits potential as a natural therapeutic agent for modulating estrogen and progesterone receptor activity as well as FSH levels. These findings support its potential use in managing hormone-related disorders, such as menopause and other reproductive health issues, offering a plant-based alternative to conventional hormone therapies. Further research is needed to fully understand its mechanisms of action and clinical applications.

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Case Series

A Case Series on Pregnant Patients with Ovarian Cysts and Management of Potential Complications

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Abstract

Objective: This case series aims to present and analyze three cases of pregnant patients with ovarian cysts, highlighting different complications that arose during their pregnancies and discussing management approaches.

Methods: We present three cases of pregnant patients with ovarian cysts diagnosed at different trimesters of gestational age. Patients included in this case series were shown to have cysts at the time of sonographic examination.

Case: Each case displayed different complications which includes constipation, urinary hesitancy, ovarian cyst torsion, and arrest of descent during in labor, which underwent specific management for each complication which includes elective cystectomy, emergency laparotomy and emergency cesarean section, respectively. All patients were discharged in clinically stable conditions and the mass was evaluated for further histopathologic examination. Follow up for histopathologic examinations revealed benign ovarian cysts (ovarian mature teratoma and serous cystadenoma) in all cases. This case series will also discuss possible complications of pregnancy with ovarian cysts, and the prevalence of each complication based on the gestational age. Due to its potential complications, ovarian cysts in pregnancy must be accurately evaluated and given appropriate management.

Conclusion: Ovarian cysts in pregnancy must be evaluated accurately so that appropriate management is carried out. Clinicians should be aware of cyst complications during pregnancy.

Keywords: Ovarian Cysts, Pregnancy, Potential Complications.

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INTRODUCTION

Ovarian cysts are liquid-filled structures that might be simple or complex. They are normal discoveries typically found unexpectedly on actual assessment or imaging. Ovarian cysts may result in rupture, hemorrhage, and torsion, which are viewed as gynecological emergencies. Accordingly, it is fundamental to immediately diagnose and manage it to avoid patient mortality. [1]

There are several variants of ovarian cysts in pregnancy, theca-lutein cyst is one of the most common ovarian cysts in pregnancy resulting from the increase in human chorionic gonadotrophin (hCG) hormone in the cases of molar pregnancy or fetal hydrops. [2] Hyperreactive luteinalis (HL) is the second most common ovarian cyst in pregnancy, which is often associated with the trophoblastic disease. [3] In addition, there is luteoma which is a mass in the ovaries and is associated with the condition of ovarian hyperstimulation and polycystic ovaries should be suspected in cases with a previous history of infertility. Other ovarian cysts variants including dermoid cysts, adenoma cysts, functional corpus luteal cysts, and endometrioma are the most common benign causes of ovarian cysts in pregnancies. [4,6]

Ovarian masses or cysts during pregnancy should be further evaluated for indications of surgical intervention. Ultrasonography (USG) and Magnetic Resonance Imaging (MRI) are preferable diagnostic modalities to distinguish benign or malignant conditions. Laparoscopic

interventions or open surgery can be performed based on tumor diameter, gestational age, and operator skill level. [5]

Most adnexal masses are diagnosed accidentally in the first trimester. It is estimated that 65-80% of cases are asymptomatic and almost 75% recover spontaneously. Borderline ovarian tumors and mature ovarian teratoma are most commonly diagnosed with histopathological examination. [6]

CASE 1

A 35-year-old pregnant woman (5-gravida, 3-para, 1-abortus), with a previous history of cesarean section in 2017 due to Fetal bradycardia and 1 day history premature ruptured of membranes, came to our clinic with a chief complaint of an enlarged abdomen and epigastric pain in the past 2 months before admission. Patient complaints are accompanied by difficulty defecating and urinating. Ultrasonography examination (Figure 1) revealed a singleton living intrauterine fetus at 11-12 weeks of gestational and a multiloculated hypoechoic mass originated from the adnexa with a solid part measuring 13.86 x 10.06 cm, suspected to be mixed solid-cystic ovarian neoplasms. The patient is educated on pregnancy conservation, follow-up tumor marker analysis, and routine sonography examinations. Elective laparotomy cystectomy was planned at 18-20 weeks of gestation. Histopathologic examination revealed ovarian mature teratoma.

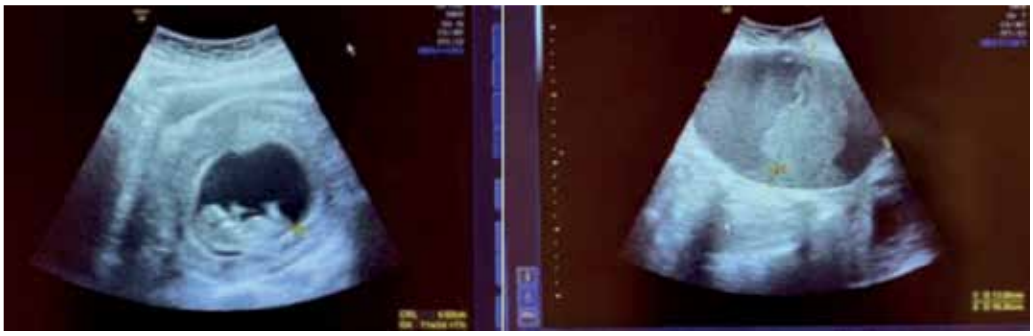

Figure 1. Ultrasonography from Case 1 revealed a singleton living intrauterine fetus at 11-12 weeks of gestation with a multilocular hypoechoic mass

CASE 2

A 19-year-old primigravida woman at 38-39 weeks of gestation came to our clinic with a complaint of persistent labor pain and bloody show on the past 1 day before admission, she also felt a decrease in fetal movement. The patient was further diagnosed with the dystocia of labor (prolonged active phase) and fetal tachycardia due to persistent 4-5 cm of cervical dilatation in observed 4 hours and an increase in fetal heart rate of 170-175 beats per minute respectively. The patient has no previous history of antenatal care during the first and second trimesters, and has no previous medical history. The vital signs of the patient were unremarkable. Abdominal examinations revealed a large fundal height of 37 cm, despite only having a singleton living intrauterine fetus with relatively smaller estimated fetal weight of 2900-3000 grams in ultrasonography. Ultrasonography (Figure 2) also revealed an uninoculated hypoechoic mass, measured 14.2 cm x 9.4 cm originating from the right adnexa. Consequently, the patient was managed with intrauterine resuscitation and prepared for emergency cesarean section with unilateral salpingo-oophorectomy. During the procedure, a female baby was born with a birthweight of 2950 grams and an APGAR of 5-6, a cystic ovarian mass sized approximately 14 x 9 cm was also evacuated and sent for a histopathologic examination (Figure 2). The left ovary and fallopian tube are visibly within normal appearance. The patient's postoperative condition and recovery were stable and within normal limits. Histopathologic examination revealed ovarian mature teratoma.

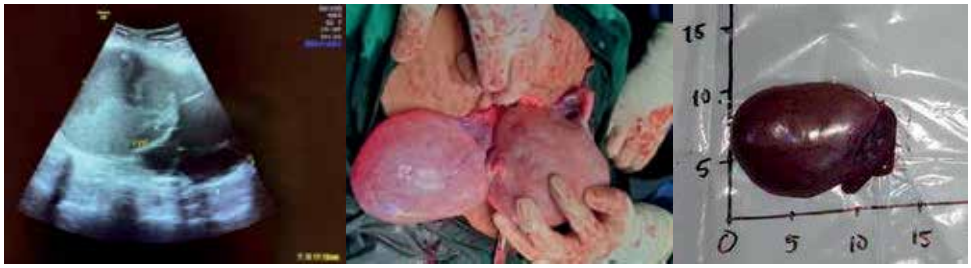

Figure 2. Ultrasonography and Gross Appearance of Ovarian Mass from Case 2

CASE 3

A 32-year-old pregnant woman (4-gravida, 3-para, 0-abortus) at 25-26 weeks of gestation came to our clinic with an acute episode of abdominal pain that radiates through the lower left abdomen 6 hours before admission (Visual Analogue Pain Scale 8-9). The patient has been diagnosed with an ovarian cyst 3 months before admission at the previous clinic. The vital signs of the patient were within normal limits. Ultrasonography examination (Figure 3) revealed a singleton living intrauterine pregnancy with a multiloculated hypoechoic mass sized with visible abdominal free fluid in the rectovaginal space with color doppler examination revealing a positive whirlpool sign suggesting ovarian cyst torsion. Emergency laparotomy-unilateral salpingo-oophorectomy was performed for the patient, and a cystic ovarian mass sized approximately 15 x 12 cm was evacuated and sent for histopathologic examination (Figure 3). The left ovary and fallopian tube are normal. Histopathology examinations revealed ovarian serous cystadenoma.

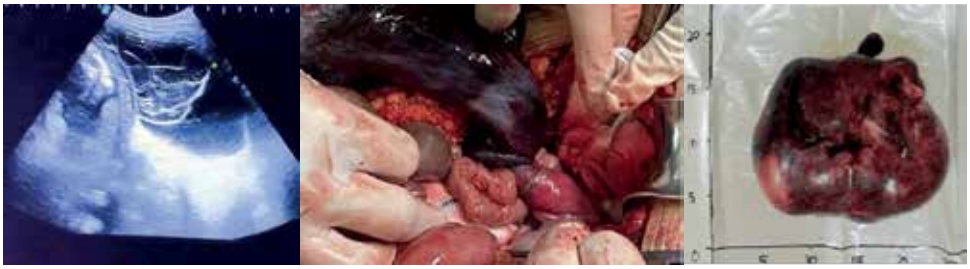

Figure 3. Ultrasonography and Gross Appearance of Ovarian Mass and Torsion from Case 3

Table 1. Summary of all three cases with patient and case characteristics, and treatment

Case No.	Patient Characteristics	Case Characteristics	Treatment
Case 1	1. 35-year-old 2. G5, P3, A1 3. Gestational Age 11-12 weeks	1. Cyst Discovery: 1st Trimester 2. USG Mass Characteristics: multiloculated hypoechoic mass, 13.86 x 10.06 cm suspected to be mixed solid-cystic ovarian neoplasm 3. Potential Complication: Spontaneous Abortion	Routine USG Elective Laparotomy Cystectomy At 18-20 weeks Of Gestation
Case 2	1. 19-year-old 2. G1, P0, A0 3. Gestational Age 37-38 weeks	1. Cyst Discovery: 3rd Trimester 2. USG Mass Characteristics: uninoculated hypoechoic mass, 14.2 cm x 9.4 cm 3. Potential Complication: Uterine Inertia (as occurred in the case)	Emergency Cesarean section With Salpingo-Oophorectomy
Case 3	1. 32-year-old 2. G4, P3, A0 3. Gestational Age 25-26 weeks	1. Cyst Discovery: 2nd Trimester 2. USG Mass Characteristics: multiloculated hypoechoic mass, 15,5 x 12,5 cm with visible abdominal free fluid in the rectovaginal space suggesting ovarian cyst torsion. 3. Potential Complications: Ovarian Cyst Torsion (as occurred in the case)	Emergency Laparotomy Salpingo-Oophorectomy

Table 2. Incidence of Potential Complications of Ovarian Cysts in Pregnancy[7,8]

Potential Complications	Incidence
Torsion	• 5% of pregnant women with mass • 20% of pregnant woman with mass > 6 cm
Rupture	• 0,5%
Malignancy	• 0,02 to 1% • Ovarian Cancer 1 : 12.500 pregancy
Preterm Delivery Abortion	• 5,8% - 10,4% • 0 - 6%

DISCUSSION

In general, ovarian mass in pregnancy is diagnosed accidentally during a routine sonographic examination. Ovarian mass detection has been significantly reciprocal with routine sonographic pregnancy screening. It was roughly estimated that ovarian mass was discovered in 1 per 76 to 2328 pregnancies, most often discovered during the second trimester, and spontaneously regress in 65-80% of cases. Resection of persistent ovarian mass is carried out to prevent potential complications such as torsion, rupture, birth obstruction, and malignancy. [5,8,9]

Ovarian cysts are the most abundant ovarian mass in pregnancy. Corpus luteal cysts incidence reaches 13 to 17% of cases in pregnancy, it produces progesterone and usually lasts 8-9 weeks of gestation before spontaneously resolving. Other types of ovarian cysts in pregnancy may include hemorrhagic cysts or endometrioma and dermoid cysts, which are most likely to form after 16 weeks of gestation. The incidence of ovarian malignancy in pregnancy reaches to one in every 12,000 to 47,000 cases and is considered the second most common mass after benign gynecological masses, and dysgerminoma is the most common malignancy found in pregnancies[5,9].

Potential complications of ovarian cysts in pregnancy include spontaneous abortion, ovarian cyst torsion , cyst rupture, malignancy, and preterm delivery (Table 2).[7,8] Spontaneous abortion in pregnancy may occur due to hemorrhagic cysts or endometrioma/endometriosis, this condition occurs as the quality of the embryo decreases due to maternal immunity factors, thereby reducing the embryonic clinical outcomes.[10,11,12]

Ovarian cyst torsion in pregnancy occurs in an estimated five cases per 10,000 pregnancies and has both high mortality and morbidity rate. Torsion more commonly occurs in the left tubal-ovarian side as opposed to the right side with an incidence ratio of 3:2, and most commonly occurs at approximately 6-14 weeks of gestation due to corpus luteal cysts.[13]

Cyst rupture in pregnancy commonly occurs during the delivery process in corpus luteal cysts and endometrial cysts due to their thinner wall structure. During labor, abdominal-fetal pressure, uterine contractions after childbirth, adhesion between tumor and uterus, external fundal pressure *(Kristeller maneuver),* and postpartum fundal massage also increases the risk of cyst rupture. Decidualization during pregnancy can affect endometrial cysts resulting in softening making them more likely to rupture. The diagnostic process of is often complicated due to overlapping labor pain and further signs of postpartum ileus. Bleeding in the corpus luteum is a rare complication that occurs more frequently in younger women, especially when associated with pregnancy.[14,15]

The existence of pelvic mass/cyst can also be responsible for labor dystocia through obstruction the descent of the presenting fetal part. Several studies of mass size in adnexa obstructed the labor process, thus inhibiting delivery.[16]

The decision to perform surgical or conservative management has to consider both maternal and fetal factors. Surgical procedures in pregnant patients with cysts may carry its own intraoperative and perioperative risks. Acute conditions such as torsion, rupture, and obstruction of childbirth require immediate surgical management. Prevoiously showed that women who underwent emergency surgery had a much higher risk of preterm labor (22% vs. 3.8%). Conservative management of ovarian mass during pregnancy may be an acceptable option in some cases. It is estimated that 71% of

the ovarian mass is benign and spontaneously regresses, while the incidence of malignant ovarian mass in pregnancy is very low (0-3% cases). Therefore, surgical management can be postponed in favor of conservative management in simple ovarian mass (< 5 cm diameter) or in complex asymptomatic ovarian mass. If the mass discovered during the first-trimester ultrasonography does not show malignancy, therefore it is necessary to carry out a further evaluation at 18-22 weeks of gestation. If the mass is discovered during the second trimester then a re-examination is carried out at 32-36 weeks gestation.[7,17,18]

In cases of complex ovarian masses that cannot be ascertained to be benign in origin by imaging, surgical management can be performed. Ultrasound features of malignant ovarian masses such as the presence of pelvic free fluid, solid components, papillary appearance, large multiloculated tumors, internal septa, and vascular nodules, should be suspected as malignancies and require surgical intervention.[7]

CONCLUSION

Ovarian cysts in pregnancy must be evaluated accurately so that appropriate management is carried out. Ultrasound examination can further evaluate diagnosis. The surgical management which includes open laparotomy or laparoscopic surgery must be performed as indicated. Clinicians should be aware of cyst complications during pregnancy such as spontaneous abortion, rupture, bleeding, and ovarian cyst torsion.

Data Availability

The data is collected from medical records and is not available for readers due to patient security.

Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this article.

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Ethical Approval

This study was approved in accordance with the Declaration of Helsinki (1964) by the Ethical Review Agency in Sam Ratulangi University, Manado, Indonesia. Verbal and written consent to publish the data was obtained from the patients.

Authors' Contributions:

Gezta N. Hermawan as the primary author collected the data on all cases. Bismarck J. Laihad analyzed all the patient findings together and revised he manuscript. All authors approved the final version.

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Case Report

Management of Severe Preeclampsia with Anemia in Pregnant Women with Covid-19 Infection : A Multidisciplinary Approach

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Abstract

Objectives: to explain the management of severe preeclampsia accompanied by anemia in pregnant women with Covid-19 Infection.

Methods: This study is a case study. The data collection process uses medical records obtained from dr. Soebandi Hospital. The data will be presented in the form of a description of the management of severe preeclampsia accompanied by anemia in pregnant women with COVID-19 Infection.

Result: In this study, we report a case of COVID-19 in a 31-year-old pregnant woman at 30-31 weeks of gestation, who is pregnant with her second child and complained of leaking amniotic fluid and shortness of breath. Physical examination results showed : positive SARS-CoV-2 antigen swab test, BP 156/112 mmHg, T (36.0°C), heart rate 107 beats per minute, respiratory rate 30 breaths per minute, fetal heart rate 144 beats per minute, SpO2 97%, urine protein +4, Hb 5.2 g%. Vaginal toucher examination revealed cervical dilation of 1 cm, negative for amniotic fluid leakage, and cephalic presentation. A spontaneous delivery occurred. A female baby was born with an APGAR score of 1-2, weighing 900 grams, a leght of 27 cm, and a normal anus. Accompanying complication include pneumonia, metabolic acidosis, anemia, melena and coagulopathy.

Conclusion: Abnormal laboratory results in pregnant women with COVID-19 can indicate the severity of the condition. So, body immunity is very important to support pregnancy and fetal growth. When the body's protection is low, the body's immunity will weaken.

Keywords: Anemia, Covid-19, Pregnancy, Severe Pre-eclampsia.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), or commonly known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), is a virus that has spread almost worldwide. COVID-19 first emerged in Indonesia on March 2, 2020, rapidly spreading throughout the country, capable of infecting the entire population, especially vulnerable groups. Pregnant women are a vulnerable group to experience health disorders, particularly infectious diseases, due to changes in their body's physiology and immune response mechanisms[1]. SARS-CoV-2 infection during pregnancy stimulates increased expression of proinflammatory cytokines such as IL-6, IL-12, IL-1β, and IFNγ, which can damage the lungs. The dominance shift to Th2 responses allows anti-inflammatory cytokines to counterbalance the expression of proinflammatory cytokines [1] , such as IL-6, which has been shown to cause severity and death in COVID-19 patients. This is why the severity of COVID-19 in pregnant women tends to be lower [2].

Anemia and Severe Pre-Eclampsia (PEB) during pregnancy can increase the risk of Covid-19 infection. Laboratory examination results of pregnant women with anemia indicate that SARS-CoV-2 infection can worsen the condition of anemia. Findings show that Covid-19 infection in pregnant women with anemia can decrease red blood cell count, hemoglobin, ferritin, serum iron, transferrin saturation, and reticulocyte count, while increasing white blood cell count and

haptoglobin levels [3]. Covid-19 infection can also trigger the occurrence of Pre-Eclampsia during pregnancy. During pregnancy, the physiological expression of angiotensin-converting enzyme-2 (ACE-2) receptors increases, particularly at placental sites. Whereas coronaviruses can bind to ACE-2 to enter human cells, causing dysregulation of the renin-angiotensin-aldosterone system and altering the ratio between angiotensin-II and angiotensin-1-7, leading to manifestations that may predispose to preeclampsia. Furthermore, cytokine storms cause endothelial dysfunction, vasculopathy, and thrombus formation, which also occur in preeclampsia [4].

Laboratory tests such as hematological examinations play a crucial role as a screening tool for patients potentially progressing towards COVID-19. Hematological changes, such as in leukocytes (lymphocytes, eosinophils, neutrophils), can depict infectious processes or indicate the severity level of infection [5]. In this study, we will report a case of Covid-19 in a pregnant woman with Severe Pre-Eclampsia (PEB) and Anemia. PEB and Anemia are pregnancy complications that may be experienced by every pregnant woman, and these conditions can be exacerbated when the pregnant woman is infected with Covid-19. This case report will provide clinical information related to pregnancy cases with Covid-19 and the accompanying complications. The aim of this study is to identify the clinical symptoms experienced by pregnant women with Severe Pre-Eclampsia and the complications associated with pregnant women infected with Covid-19.

CASE DESCRIPTION

A 31-year-old woman, pregnant with her second child, presents with Severe Pre-Eclampsia (PEB) and Anemia. The patient arrived at the hospital accompanied by a midwife, complaining of shortness of breath and leaking amniotic fluid. The midwife's examination already showed cervical dilation (1 cm). Upon arrival at the hospital, a swab antigen test was performed and returned positive for SARS-CoV-2. The patient had been attending regular antenatal visits. In terms of medical history, the patient reported no previous underlying health conditions.

Physical examination revealed high blood pressure (abnormal), tachycardia (heart rate 107 beats per minute), and abnormal breathing (signs of respiratory distress). Initial examinations included a complete blood count and blood biochemistry panel. The results showed leukocytosis, lymphopenia, and abnormal hematocrit levels.

The patient received collaborative care between an obstetrician and an internal medicine specialist. Based on the consultation with the obstetrician, the patient was advised to undergo hemodialysis and receive $MgSO_4$ therapy. Meanwhile, based on the consultation with the internal medicine specialist, the patient was advised to receive cefuroxime and remdesivir treatment.

The delivery process was spontaneous. A female baby was born, with an APGAR (AS) of 1-2, weighing 900 grams, length of 27 cm and confirmed to have an anus.

RESULTS

Physical examination results revealed blood pressure of 156/112 mmHg, temperature (38.0°C), heart rate of 107 beats per minute, respiratory rate of 30 breaths per minute, SpO2 of 97%, urine protein of +4, hemoglobin of 5.2 g%, and fetal heart rate of 144 beats per minute. Vaginal toucher examination showed cervical dilation of 1 cm, negative for amniotic fluid leakage, and cephalic presentation. Laboratory examination results showed leukocytes 17.2, segmented neutrophils 91%, lymphocytes 5%, monocytes 4%, hematocrit 15%, and platelets 71 x 10^3 uL. Complications during the patient's treatment included pneumonia, metabolic acidosis, anemia, melena, and coagulopathy. It is occurred after the patient received treatment in the hospital (two days in the hospital).

Table 1. Frequency distribution of physical examination results in pregnant women with Severe Pre-Eclampsia (PEB) and Anemia

Category	Examination Result	Normal Value	Conclusion
Blood Pressure	156/112 mmHg	<120/80 mmHg	Hypertension
Temperature	38.0°C	36.5°C - 37.5°C	Hyperthermia
Heart Rate	107 beats/min	60-100 beats/min	Tachycardia
Respiration Rate	30 breaths/min	12-20 breaths/min	Tachypnea

From table 1, we can observe the physical examination results in this case show an increase in blood pressure, namely 156/112 mmHg, indicating hypertension; an increase in body temperature to 38.0°C, indicating hyperthermia; an increase in heart rate to 107 beats per minute, indicating tachycardia; and an increase in respiration rate to 30 breaths per minute, indicating tachypnea.

Table 2. Frequency distribution of laboratory examination results in pregnant women with Severe Pre-Eclampsia (PEB) and Anemia

Category	Examination Result	Normal Value	Conclusion
Hb	5.2 gr%	>11 gr%	Anemia
Hematocrit	15 %	40-50 %	Low/Anemia
Monocytes	4 %	2-8 %	Normal
Lymphocytes	5 %	20-40%	Lymphopenia
Segmented Neutrophils	91 %	50-70 %	High
Leukocytes	17.2 x 10^3 uL	5.0-10.0 x 10^3/µl	Leukocytosis
Platelets	71 x 10^3 uL	150-400 x 10^3/µl	Thrombocytopenia
Urine Protein	+4	Negative	Pre-Eclampsia
SGOT	85	5-40 IU/L	High
SGPT	93	7-56 IU/L	High

From table 2, we can observe the laboratory examination results in this case show Anemia is detected with a Hemoglobin level of 5,2 gr%, supported by a low hematocrit level indicating anemia. There is a decrease in lymphocytes (5%) indicating lymphopenia, and an increase in leukocytes (17.2 x 10^3/µl) indicating leukocytosis. There is decrease in platelets (71 x 10^3 uL) indicating thrombocytopenia. One indicator of coagulopathy is platelet count (Thrombocytopenia). Additionally, urine protein is detected at +4, indicating Severe Pre-Eclampsia.

DISCUSSION

SARS-CoV-2 and Pregnancy

Pregnant women are a vulnerable group to experience health disorders, especially infectious diseases, due to changes in their body's physiology and immune response mechanisms [6]. SARS-CoV-2 can infect pregnant women from early pregnancy or the first trimester to the third trimester. In the early stages of pregnancy, SARS-CoV-2 infection has the potential to affect organogenesis and fetal development, increasing the risk of miscarriage. COVID-19 infection can lower immunity in pregnant women and may affect the flow of nutrients and oxygen to the fetus through the placenta [7]. Along with changes in gestational age, the mechanisms of adaptive immune response also change. The first trimester is referred to as the proinflammatory stage to support embryo implantation. The second trimester is referred to as the anti-inflammatory stage; this stage is crucial for maintaining fetal growth, and the third trimester is referred to as the proinflammatory stage as it approaches delivery time [8]. In this case study, it is reported that SARS-CoV-2 infection occurred in a pregnant woman in the third trimester or late trimester at 31 weeks of gestation. The late stage of pregnancy is commonly referred to as the proinflammatory stage as it approaches delivery time, and this mechanism underlies why the majority of COVID-19 cases in pregnancy occur in the late trimester [9].

Screening should ideally be conducted at the first contact with healthcare facilities, including a medical history that includes contact history, physical examination for increased temperature and respiratory rate, laboratory tests, and imaging (WHO, 2020). The clinical manifestations of COVID-19 infection during pregnancy are not different from viral infections in general. Symptoms include fever (53%), cough (42%), shortness of breath (12%), headache, and loss of smell or anosmia [10,11]. The physical examination results in this study also revealed similar symptoms to previous research, including an increased body temperature of 38.0°C, increased heart rate of 107 beats per minute, and increased respiratory rate of 30 breaths per minute.

The diagnosis of COVID-19 in pregnancy is determined similarly to non-pregnant women, based on clinical symptoms and RT-PCR testing as the gold standard diagnosis. Other supportive tests such as laboratory examinations, including complete blood count, white blood cell differential count, C-reactive

protein (CRP), and rapid antibody tests, are also recommended for screening. Increased CRP levels and decreased lymphocyte counts have been found in pregnant women with COVID-19. Calculation of the neutrophil-to-lymphocyte ratio is easy to perform and can be used as one of the screening methods, but its value is greatly influenced by conditions such as preeclampsia, HELLP syndrome, gestational diabetes, ectopic pregnancy, and hyperemesis gravidarum [10]. In this case report the results of laboratory examination were obtained showed a decrease in lymphocyte count (5%) and an increase in leukocyte count (17.2 x 10^3/µl). Other laboratory examination results revealed anemia with a Hemoglobin level of 5.2 gr%, Urine Protein of +4, indicating severe pre-eclampsia and decrease in platelets (71 x 10^3 uL) indicating thrombocytopenia.

From these examination results, it can be observed that pregnant women with Covid-19 can experience complications during pregnancy. This is because overall T-cell activity during pregnancy decreases, and T-cells increase during infection. This relates to the function of T-cells, which can attack virus-infected cells. CD8+ T-cells during pregnancy remain at normal levels. CD8+ cells, which have cytotoxic properties, increase their activity when pregnant women are infected with a virus. This result is associated with the theory that cellular immune responses are more active during viral infections. Studies investigating exhausted T-cells, which are T-cells that have been repeatedly exposed to antigens, have largely diminished function, and senescent T-cells, which are T-cells that have lost their ability to proliferate but can still perform their effector cell functions, also play a role [12]. Shifting Th1/Th2 occurs during pregnancy, with Th1 decreasing while Th2 increases. This is why pregnancy makes both the mother and fetus highly susceptible to infection. Th1 cells function in inflammatory conditions, while Th2 cells function in allergic mechanisms. Th1 activity creates a proinflammatory condition, whereas Th2 activity creates an anti-inflammatory condition [12].

SARS-CoV-2 and Pre-Eclampsia

Preeclampsia is a condition that complicates pregnancy, posing significant risks to the health of both the mother and the fetus, and may result in induced preterm delivery. Preeclampsia occurs in approximately 2–4% of pregnancies, and its exact etiology remains not fully understood. However, it is believed to involve maternal vascular malperfusion and cardiovascular maladaptation due to an imbalance of angiogenic factors, endothelial dysfunction, coagulopathy, and inadequate complement regulation [13]. Pregnant women infected with COVID-19 have a 4.045 times higher risk of developing preeclampsia compared to those who are not infected. Previous studies have indicated a significant relationship between COVID-19 infection and the occurrence of preeclampsia [14].

Pregnant women are particularly vulnerable to COVID-19 infection due to an increase in ACE2 receptors, especially in the placenta. The coronavirus binds to ACE2 to enter human cells, causing dysregulation of the renin-angiotensin-aldosterone system and an imbalance in the ratio between angiotensin-II and angiotensin-1-7, inducing manifestations resembling preeclampsia. The binding of the virus to ACE2 downregulates the conversion of angiotensin II to angiotensin I, leading to increased levels of angiotensin II. This results in endothelial dysfunction, vasculopathy, and thrombus formation, which are also observed in preeclampsia [15]. From the explanation above, it is evident that both the mother and fetus are highly vulnerable to infection. Therefore, a pregnant woman must maintain her health by adopting a clean and healthy lifestyle, as her body's defenses are inadequate to fully perform various physiological functions. The immunity of a pregnant woman can attack the fetus if she is in an inflammatory condition. This could disrupt fetal development, cause permanent abnormalities in the fetus, and even lead to miscarriage due to inflammatory processes [10].

Preeclampsia is characterized by elevated blood pressure and the presence of protein in the urine and is associated with various hematological changes, particularly those affecting the coagulation cascade. Thrombocytopenia, or a low platelet count, is the most common hematological abnormality in preeclampsia and eclampsia [16]. In this case, the pregnant woman's blood pressure was recorded at 156/112 mmHg (hypertension), urine protein was +4 (preeclampsia), and platelets were 71 x 10^3/µL (thrombocytopenia). Hypertension in pregnancy is defined as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg measured twice, 4 hours apart, while at rest. Hypertension is a diagnostic criterion required for the preeclampsia syndrome. Proteinuria in preeclampsia results from increased permeability of the renal tubules

to large molecular weight proteins such as albumin, globulin, transferrin, and hemoglobin. Proteinuria may take up to 2 years to resolve after preeclampsia, with the severity of preeclampsia and time to delivery positively correlated with recovery time. Thrombocytopenia (platelets <100,000) is likely caused by increased platelet activation, aggregation, and consumption. It has been hypothesized that syncytiotrophoblasts release extracellular vesicles that enhance platelet activation, leading to the release of soluble factors and extracellular vesicles, which may contribute to placental and systemic microvascular ischemia [17].

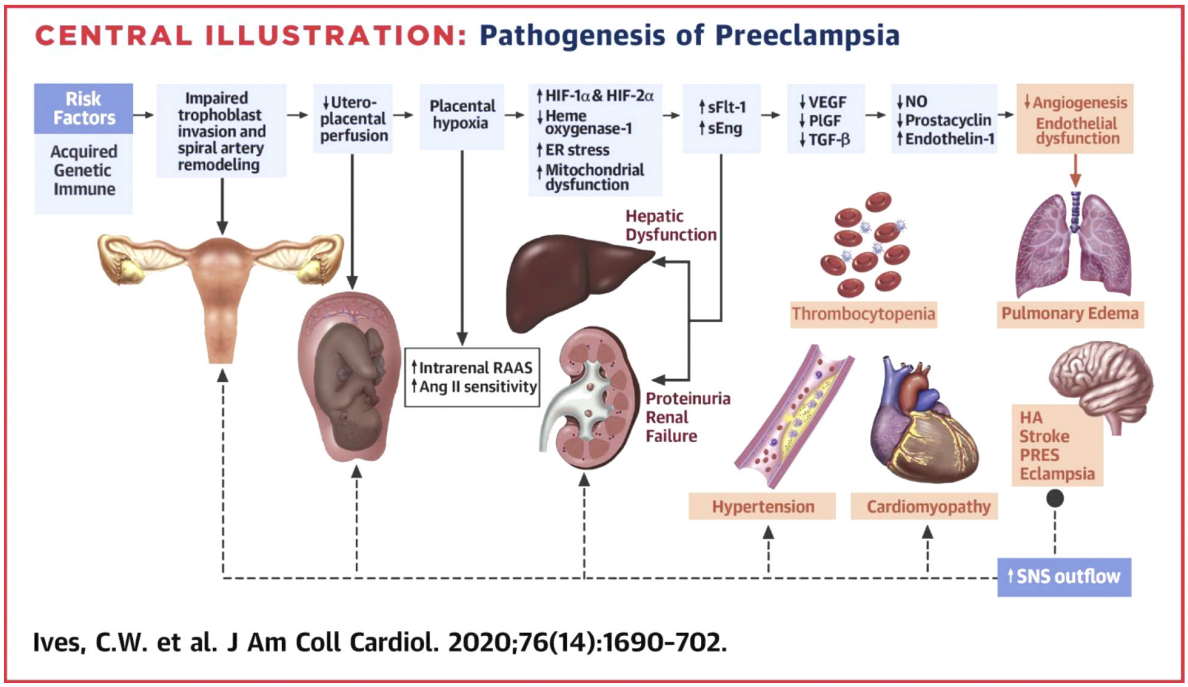

Figure 1. Acquired, genetic, and immune risk factors contribute to early placental dysfunction (Stage 1). Placental dysfunction results in the release of antiangiogenic factors, leading to later multiorgan dysfunction (Stage 2). Solid arrows indicate disease progression. Dashed arrows indicate SNS effects on respective organs. Ang II = angiotensin II; ER = endoplasmic reticulum; HA = headache; HIF = hypoxia-inducible transcription factor; NO = nitric oxide; PlGF = placental growth factor; PRES = posterior reversible encephalopathy syndrome; RAAS = renin-angiotensin-aldosterone system; sEng = soluble endoglin; sFlt = soluble fms-like tyrosine kinase; SNS = sympathetic nervous system; TGF = transforming growth factor; VEGF = vascular endothelial growth factor.

SARS-CoV-2 and Anemia

The immunological and hematological changes during pregnancy increase the risk of COVID-19 infection and anemia in pregnant women [18]. COVID-19 infection in pregnant women can affect hemoglobin (Hb) levels and directly attack the respiratory system, leading to respiratory failure and hypoxia. Hypoxia triggers inflammation and disrupts iron metabolism, making it difficult for the body to absorb iron. This results in decreased iron availability for erythropoiesis, worsening anemia in pregnant women, and potentially causing multi-organ dysfunction syndrome in pregnant patients with COVID-19. This occurs because COVID-19 infection exacerbates anemia [19].

When the COVID-19 virus attacks the immune system, the innate immune response activates hepcidin. Hepcidin is the primary regulator of iron entry into the bloodstream and functions by inhibiting ferroportin. Ferroportin is a transmembrane protein responsible for transporting iron out of cells. Its inhibition traps iron within reticuloendothelial macrophages, ultimately reducing Hb levels in the blood. Furthermore, COVID-19 can attack the respiratory system, causing the lower respiratory tract to release pulmonary infiltrates, which worsens oxygen and carbon dioxide circulation. As the virus enters through the respiratory system, it can cause respiratory failure, leading to hypoxia. This triggers inflammation and changes in iron metabolism, further reducing Hb levels in the blood and leading to anemia [19].

Previous study states that without sufficient iron, the body cannot produce hemoglobin to form red blood cells, which leads to anemia.

Anemia causes an increase in corticotrophin-releasing hormone (CRH) synthesis due to tissue hypoxia, which then results in uteroplacental insufficiency and disrupts blood supply to the fetus. This aligns with the theory of placental ischemia in the pathophysiology of preeclampsia. Ischemic and hypoxic placenta stimulates the formation of oxidants/free radicals, which can damage cell membranes rich in unsaturated fatty acids, leading to lipid peroxidation (20).

CONCLUSION

Abnormal laboratory results in pregnant women with COVID-19 can indicate the severity of the condition. These laboratory findings can help determine prognosis early on, allowing for early intervention in the hope of improving the patient's condition. COVID-19 virus infection in pregnant women can increase the risk of complications during pregnancy. This is because pregnant women are considered a vulnerable group experiencing physiological changes in their bodies and alterations in their immune response.

CONFLICT OF INTEREST

This research is a personal study funded internally by Universitas dr. Soebandi, and there are no conflicts of interest in this research.

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Case Report

Multiple Congenital Anomalies with Breech Presentation: Dilemma in Diagnostic Procedures, Delivery Management, and Counseling in Developing Country

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Abstract

Introduction: Multiple congenital anomalies present significant diagnostic and management dilemmas, particularly in resource-limited settings. Globally, these conditions affect approximately 1 in 33 infants and are a major contributor to perinatal mortality. We report a rare case of a term pregnancy with severe, undiagnosed multiple congenital anomalies, highlighting the challenges in diagnosis, delivery management, and counseling in a developing country.

Case Illustration: A 22-year-old primigravida presented at 35-36 weeks of gestation in active labor with a fetus in breech presentation. Antenatal ultrasonography at 27 weeks had revealed a single live fetus with severe fetal growth restriction, polyhydramnios, and multiple structural anomalies suspicious for an underlying trisomy. Amniocentesis was offered for a definitive diagnosis but was declined by the family. A female neonate was delivered via spontaneous vaginal breech delivery, with low APGAR scores. The infant was admitted to the High Care Unit for respiratory support but passed away the following day due to respiratory failure. The family had opted for a Do Not Resuscitate (DNR) status.

Conclusions: In cases of severe fetal anomalies detected by ultrasound, advanced genetic testing like NIPT followed by diagnostic testing should be offered to facilitate definitive diagnosis and counseling. Delivery decisions in such cases should be individualized, prioritizing maternal safety while considering the fetal prognosis. This case underscores the urgent need for improved access to and awareness of genetic counseling and diagnostic services in developing countries to optimize perinatal outcomes.

Keywords: multiple congenital anomalies , breech presentatoin, prenatal diagnosis, genetic counceling, developing countries.

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INTRODUCTION

Severe congenital abnormalities represent a significant global health challenge, profoundly impacting perinatal and infant mortality as well as morbidity throughout infancy and childhood. Globally, the World Health Organization (WHO) estimates that major congenital anomalies affect approximately 1 in 33 infants, contributing to hundreds of thousands of neonatal deaths annually. [1] In developing countries like Indonesia, these conditions are a leading cause of infant mortality, underscoring the critical need for effective prenatal detection and management.[2] These conditions are known to affect at least 2% of fetuses and newborns.[3-5] Over the past few decades, ultrasonography examinations have become a cornerstone in identifying a growing number of these defects during pregnancy. An effective prenatal diagnosis offers several benefits, such as optimizing prenatal care management, connecting pregnant women with the appropriate level of care, and planning the baby's postnatal care.[6,7] While many fetal defects have been attempted to be corrected intrauterine, the results have not been consistently satisfactory thus far.[3-7]

The foundation of first- and second-trimester screening for common genetic disorders is fetal observation through ultrasound, complemented

by maternal biomarkers and genetic testing. Since the advent of non-invasive prenatal testing (NIPT), which sequences cell-free fetal DNA, the diagnostic rate for common trisomies and sex chromosomal aneuploidies has significantly increased.[6,7] However, as its usage grows, the optimal ways to integrate NIPT into prenatal care are becoming less clear, a situation complicated by a lack of understanding among clinicians and families regarding the test's limitations, particularly in complex congenital anomaly cases. Moreover, the role and accessibility of such advanced testing in developing countries remain debated.[6,7]

Herein, we report a rare case of a 35-36 week gestation pregnancy with a fetus in breech presentation, complicated by polyhydramnios and multiple congenital anomalies (micrognathia, hypotelorism, low set ear, bilateral club hand with clenched hand, and bilateral club foot) suspicious for an underlying trisomy. The breech presentation itself is considered a potential marker for congenital anomalies.This case highlights the critical dilemmas in diagnostic procedures, delivery management, and patient counseling within a developing country's healthcare system. Therefore, this study aims to report a case of severe multiple congenital anomalies and discuss the associated challenges in diagnosis, management, and counseling.

CASE ILLUSTRATIONS

This following case was described according to the CARE checklist. A-22 years old G1P0A0 felt 8 months pregnant came to obstetrics and gynecology ward for pregnancy control. The patient acknowledged complaints of labor pain that became more frequent and stronger started from one day before admission accompanied by bloody show. Complaints of profuse discharge from the birth canal were denied. Fetal movement was still felt by the mother. The mother discovered abnormalities in her fetus during antenatal care at 27 weeks of gestation. However, history of congenital abnormalities in her family was denied. History of consuming herbal medicines or drugs during pregnancy was denied. She had a history of living around the industrial area (garment factory) less than 50 meters away. The patient denied a history of chronic diseases such as high blood pressure, diabetes, heart disease and asthma. She also denied any history of contact with Covid-19 patients, history of fever, cough, runny nose and sore throat. She had already vaccinated three times with Sinovac.

Physical examination revealed a normal result. External obstetric examination showed gestational age based on fundal height was the same as gestational age based on her last menstrual period with breech fetal position. Her uterus was not contracted adequately and her fetal heart rate detected. Initial laboratory findings on admission were within normal limits for a patient in labor, with a hemoglobin level of 14.4 g/dL, a leukocyte count of 14,540/µL, and a platelet count of 279,000/µL. Cardiotocography (CTG) monitoring revealed a baseline fetal heart rate of 140-150 beats per minute (bpm), moderate variability, and the presence of accelerations, with no decelerations. The tracing was classified as a Category I fetal heart rate pattern.

Maternal-Fetal ultrasonography (18/12/2023) or about 8 weeks before admission, demonstrated a single intrauterine alive fetus, in breech position; according 27-28 gestational weeks (27^{+3} weeks), estimated fetal weight (EFW) of 1041 grams (percentile <1%), fetal heart rate (+) ; Face: nasal bone (+), Nostril (+), Cleft (-), micrognathia (+), hypotelorism (+) (5th percentile 1.8 cm); Thorax: four-chamber view (4CV) findings were within normal limits; CTAR 15%, Axis 49.66 degrees; Abdomen: Minimally filled stomach, normal filled urinary bladder; both kidneys are visualized normally; Amniotic fluid with single deepest pocket (SDP) 11.69 cm. The placenta was inserted posteriorly and extends laterally. Notably, a hypoechoic clear zone measuring 2.25 cm x 1.36 cm was identified at the umbilicus. This finding raised suspicion of a ventral wall defect such as an omphalocele, which further added to the diagnostic complexity of the case. Superior extremity: HL, radius and ulna corresponding 26-27 weeks, bilateral club hands (+), clenched hands (+); Inferior extremities: bilateral club feet with suspected bilateral rocker bottom feet. From velocimetry doppler findings, umbilical artery pulsatile index 1.15 S/D 3.34; middle cerebral artery pulsatile index (MCA PI 1.34 S/D 3.47); right uterine artery pulsatile index 1.37: left uterine artery pulsatile index 0.77 with notching -/-. Ductus venosus revealed normal flow. All these findings suggest a pregnancy of 28-29 gestational weeks (18/12/23) and 35-36 weeks at current admission; breech position; polyhydramnios with multiple congenital anomalies (micrognathia, hypotelorism, low set ear, club hand bilateral with clenched hand,

club foot bilateral); arthrogryposis suspect of trisomy **(Figure 1)**. For diagnostic purpose, the patient was suggested for amniocentesis after a scheduled multidisciplinary consultation for congenital anomalies at Hasan Sadikin General Hospital, but the patient's family refused.

Vaginal delivery was planned for this patient along with closed and regular monitoring of vital sign, uterine contraction, fetal heart rate, and labor progress. Prompt informed consent to the patient and her family regarding fetal death was performed on this patient. The following day after admission, a female baby was born with spontaneous bracht vaginal delivery with birth weight of 1514 grams and body length of 30 cm; APGAR 1 minutes and APGAR 5 minutes were 3 and 5. New Ballard Score (NBS) could not be calculated. The patient was observed for 6 hours post-partum with a good general and obstetric condition, vital sign, and no complications were found. She was discharged afterwards and was planned for outpatient treatment and given medication therapy of cefadroxil 500 mg twice daily and mefenamic acid three times a day. However, her baby was admitted to High Care Unit (HCU) installed with C-PAP (continuous positive airway pressure) as shown in **Figure 2**. During monitoring, desaturation occurred up to 25% along with increased respiratory distress increases, cyanosis in the hands and feet area with no thermolability. After her family decided to remain DNR (do not resuscitate), the patient's baby died due to respiratory failure and bradycardia as consequences of multiple congenital anomalies.

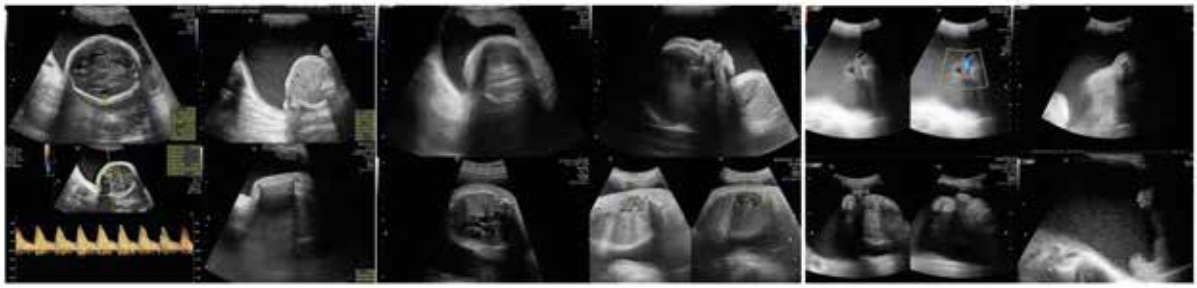

Figure 1. Maternal-Fetal Ultrasound of This Patient Revealed Multiple Congenital Anomalies.

Figure 2. Patient's Newborn with Multiple Congenital Anomalies (micrognathia, hypotelorism, low set ear, club hand bilateral with clenched hand, club foot bilateral); arthrogryposis suspect of trisomy

DISCUSSIONS

Prenatal Screening Test

At least 2% of fetuses and newborns are known to have severe congenital malformations[3-7], which significantly affect perinatal and infant mortality as well as morbidity during infancy and childhood. Over the last few decades, ultrasonography studies have been used to detect a growing variety of congenital abnormalities during pregnancy. Prenatal diagnosis serves a number of functions, including improving the likelihood of optimum pregnancy management in terms of prenatal care, referring expectant mothers to the appropriate level of care, and organizing the baby's postnatal care.7 There have been attempts to correct several fetal abnormalities intrauterine, but the outcomes have been unsatisfactory thus far.[3-7]

At first, in this case, the patient had a child with congenital abnormalities with environmental risk factors (living close to a garment factory). Previous meta-analysis study revealed that the offspring's neural tube defects (OR: 1.51, 95% CI: 1.09–2.09) and congenital heart diseases (OR: 1.31, 95% CI: 1.06–1.63) were linked to the mother's occupational exposure to solvents such as products from garment factory.8 Maternal exposure to chemicals at work before and throughout pregnancy is a significant environmental risk that has been linked to the development of congenital abnormalities. Studies that have looked at occupational exposure of mothers have mostly examined exposure to metals, pesticides, and solvents. There are a number of unfavorable reproductive outcomes linked to exposure to these chemicals. This is significant since the first month of pregnancy to the end of the first trimester is when most congenital abnormalities arise. Maternal oocytes are susceptible to chemical exposure in the month preceding conception. Chemical exposure during the first trimester of pregnancy can have an impact on the developing embryo. After this point, organogenesis is finished and and the fetus is less susceptible to chemical exposure for development.[8]

Since Non-Invasive Prenatal Testing (NIPT) was first used in a therapeutic context, there has been disagreement over the most effective way to integrate it into standard prenatal care. NIPT is optional, just like all other prenatal screening tests, and it can be carried out as early as 9 to 10 weeks of pregnancy and all the way up to term. Furthermore, depending on their insurance company, patients may have to pay for this more costly test out of cash. Massive parallel shotgun sequencing advances in genomics produced NIPT, a screen that detects cell-free fetal DNA sequences that originate in placental cells and are present in maternal blood.[9-11] In the first prospective trials, trisomy 21 was detected with 100% sensitivity and more than 99% specificity in high-risk women who underwent NIPT testing.[10] Numerous studies have consistently shown that while NIPT is quite accurate in detecting trisomies 21 and 18 but not trisomy 13 such as to confirm trisomy in this case. Posttest counseling is strongly advised for patients who receive a screen-positive result. A medical geneticist or certified genetics counselor may be consulted to discuss the necessity of prenatal diagnostic testing, such as chorionic villus sampling (CVS) or amniocentesis, or postnatal genetic testing to confirm the diagnosis. Chromosomal aberrations may be detected with a sensitivity of 99.2% (95% CI 98.9–99.6%) and a specificity of 98.5–98.8% (95% CI) using CVS and a sensitivity of 98.8% with specificity of 99.96% using amniocentesis.[12]

Every screening test that has been covered up to this point advises invasive diagnostic testing by CVS or amniocentesis in the event that abnormal results arise. However, amniocentesis takes place in the second trimester.[14] A transcervical (the more usual method) or transabdominal approach is used to extract chorionic villi cells from the placenta during CVS, which takes place between 10 and 13 weeks of gestation and is guided by ultrasound technology. During the 14–20 gestational weeks period, amniocentesis is a technique that uses ultrasound guidance to insert a needle into the amniotic sac and extract amniotic fluid. Since the amniotic fluid includes fetal cells, it can be utilized for karyotyping and genetic testing.[14]

From traditional cytogenetic analysis to next-generation sequencing (NGS), which can detect pathogenic variations from the whole human exome or genome, genetic testing techniques have advanced dramatically.[14] Genetic testing is offered at various research-based institutes in developing countries such in Indonesia, however its availability differs throughout nations. Other obstacles include a lack of knowledge among the public and health professionals, the medical genetic infrastructure—which includes legal frameworks, professional recognition, and

regulations—the limitation of national health insurance coverage, the minimum level of government support, and a lack of interest in and expertise in genetic disease research.[15]

In contrast to genetic testing, anatomical scanning by ultrasound in the second trimester has an approximate detection rate of 60%, albeit this might vary greatly depending on the ultrasonographer's skill, the woman's body mass index (BMI), the patient population in the research, and the severity of the abnormality. After a normal NIPT result, a genetic sonogram is not advised due to its poor performance in comparison to the NIPT. The degree of suspicion for both significant and small defects, as well as the criteria for anatomical scanning, will probably change if NIPT is included into standard prenatal treatment. A thorough anatomy scan is an essential component of standard prenatal care, even though a normal NIPT could be comforting in its own right.[13-15]

Thus, there is still opportunity for NIPT in this instance, which is followed by amniocentesis (during the third trimester) to confirm trisomy in severe cases of multiple congenital anomalies. Amniocentesis and genetic testing with NIPT are also advised as complementary procedures for these individuals, since the research suggests that their diagnostic value outweighs that of sonographic evaluation alone. However, cost, insurance, and the patient's socioeconomic condition also required to be considered.

Delivery Options in Fetus with Severe Congenital Anomalies in Breech Position

The baby of this patient also experienced multiple congenital anomalies in the breech position and was born via spontaneous bracht vaginal delivery. According to previous study, when compared to the cephalic presentation (3.7%), the frequency of congenital abnormalities in breech babies was twice as high (6.5%).[16] A congenital abnormality may be indicated by breech presentation at birth. Breech babies need to be examined closely in case there is any deformity. Pregnant women who have a cesarean birth are often at higher risk for infection, hemorrhage, organ damage, and particularly for infections in subsequent pregnancies. On the other hand, a cesarean delivery can also help with scheduling and support planned surgery, such as the ex-utero intrapartum therapy (EXIT) method, and lower the risk of birth damage to the fetus with specific deformities.[23] Therefore, in situations of fetal abnormalities, the advantages of a caesarean birth must be carefully considered against the possible disadvantages to the mother and should be conducted due to obstetrics indications only. Maternal risks are typically lower with an uncomplicated vaginal delivery than with a cesarean delivery.[16] Moreover, there are no previous studies that specifically mentioned the survival rate of vaginal delivery in the birth of fetuses with congenital abnormalities, especially in breech position, but a registry study shows that congenital abnormalities increase admission to the neonatal intensive care unit (NICU) or perinatal death of neonate in the labor room (LR) or operation theater (OT) with OR 34.03; 95% CI 20.51–56.46) with less mortality cases occur in labor room with vaginal delivery.[17]

Vaginal delivery in breech cases with congenital abnormalities can be carried out like vaginal delivery in breech cases in general which are: 1) Spontaneous labor (spontaneous breech) in which the baby is born with the mother's own energy. This method is commonly known as spontaneous Bracht method. 2) Manual aid (partial breech extractions; assisted breech delivery) The fetus is born partly with the energy and strength of the mother and some with helpers. 3) Breech extraction (total breech extraction) The fetus is born entirely using helper power.[16] In this patient, the baby was planned for vaginal delivery because there was no obstetrical indication to do caesarean section. Thus, vaginal delivery with spontaneous bracht was performed in this patient.

Genetic Counseling

Trisomy such in this case has been extensively researched since it is the most prevalent genetic condition in the human population. Multiple incidences of trisomy including Trisomy 21 (T21) may be detected, despite the fact that the estimated recurrence risk for trisomy in 1-2% cases.[3] Currently, the study of European amniocenteses gathered in the 1980s (Stene et al. 1984; reanalyzed by Warburton et al. [1987]) is the most common basis for genetic counseling on trisomy recurrence. Regarding trisomy 21, these data indicated that the risk of recurrence was about eight times the maternal age-associated risk for women under 30 at the time of prenatal diagnosis, whereas for women whose first trisomy occurred at age ≤30. This recurrence risk has been

explained by a number of theories, including gonadal mosaicism in the parents, age-related risk in the mother, and genetic susceptibility to nondisjunction.[3] The most plausible mechanism linked to repeated homotrisomy in the same relationship is gonadal mosaicism, particularly, and parental mosaicism, the mechanism that is most commonly described. Age-related maternal risk is assumed to be the cause of most of the remaining instances. Mosaicism is a significant factor in recurrent Trisomy, thus families who desire to obtain prenatal counseling and have several afflicted children should be suspicious of this condition.[3,19]

Rarely is gonadal trisomy 21 mosaicism explicitly documented since ovarian biopsies or germ cells are required. The percentage of mosaic cells, the tissues examined, and the quantity of cells counted would all be factors in the diagnosis of somatic mosaicism. It is advised to look for the trisomic line in at least two distinct tissue samples if mosaicism is suspected. When compared to blood-derived DNA, oral mucosa cells offer a better diagnostic yield in a noninvasive manner. It is thought that fetal oogonial/oocyte Trisomy mosaicism is the most likely cause of younger women's higher recurrence risk.[3,19]

As demonstrated in our example, there is currently only one method available for the identification of low-level/cryptic mosaicism, which involves using fluorescence in situ hybridization (FISH) technology with chromosome-specific probes on large cell populations from various tissue samples.[19] It is possible that low-level mosaicism went undetected and that the aborted fetus with mild down syndrome phenotypic characteristics was underdiagnosed based on the traditional G-banding study performed to evaluate the karyotype. It is advised to do a comprehensive cytogenetic analysis of both parents.[19,20]

The elevated recurrence risk brought on by the potential presence of undiagnosed parental mosaicism for Trisomy should be taken into consideration in genetic counseling. Gonadal mosaicism, which is usually of maternal origin, is a significant cause of recurrent Trisomy 21 and should be highly suspected in families where more than one child is afflicted. Despite living in the era of molecular diagnostics and high-resolution instruments, it is important to remember that the degree of mosaicism affects data interpretation and might result in incorrect diagnoses. Because low-level mosaicism may go undetected by traditional cytogenetic testing, FISH analysis in a large number of cells in various tissue samples, such as blood and oral mucosa cell, is essential for detecting it and is a major prognostic factor.[19,20] However lack of knowledge among the public and health professionals, lack of the medical genetic infrastructure—which includes legal frameworks, professional recognition, and regulations—the limitation of national health insurance coverage, the minimum level of government support, and a lack of interest in and expertise in genetic disease research are some obstacles of genetic testing have to be faced in Indonesia.[15] This issues become dilemmatic considering that according to Law No. 36 of 2009 regarding Health in Indonesia article 72, obtaining correct and accountable information, education and counseling regarding reproductive health is the right of every citizen. However, health insurance in Indonesia does not cover genetic examination and counseling. In fact, if genetic disorders could be screened earlier, termination can be carried out before the pregnancy reaches six weeks old (article 75 and article 76), calculated from the first day of the last menstrual period and performed by certified health workers who have the authority, determined by the minister.[21] In developing countries such as Indonesia, apart from the problem of limited funding which is not covered by health insurance, this one becomes as ethical issue related to termination of pregnancy if congenital abnormalities are detected at more than 6 weeks of age such found in this case.

The primary strength of this case report lies in its comprehensive illustration of the multifaceted dilemmas—diagnostic, management, and counseling—faced in a low-resource setting when managing a rare combination of multiple congenital anomalies with breech presentation. This report provides valuable real-world insights for clinicians in similar developing countries. However, this study has several limitations. First, as a single case report, the findings cannot be generalized. Second, a definitive genetic diagnosis could not be established as the family refused invasive testing like amniocentesis. Lastly, complete laboratory and cardiotocography data were not available due to the emergency nature of the admission, which could have provided additional clinical information.

CONCLUSIONS

In severe situations of multiple congenital

anomalies, NIPT could be performed, followed by CVS or Amniocentesis (based on patient's gestational weeks) to confirm trisomy, especially when combined with sonography findings. The method of delivering a breech patient in cases of multiple congenital anomalies could be carried out based on obstetric considerations and in this case spontaneous bracht delivery is appropriate due to survival rate of the baby. Genetic counseling is necessary in these patients given the recurrence rate in subsequent pregnancies, however, the importance in developing country is still debated.

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