

RUPTURED ECTOPIC PREGNANCY WITH LEVONORGESTREL IMPLANT : A CONTRACEPTIVE FAILURE AND LIFE-THREATENING CASE

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ABSTRACT

Levonorgestrel implant is the most used in Indonesia, it is free provided by BKKBN. Levonorgestrel implant provides 99.95% of effectiveness. However, it could not prevent pregnancy absolutely including ectopic pregnancy. Ectopic pregnancy is a lifethreatening condition that is oftenly ignored by the patient and sometimes misdiagnosed. The incidence of ectopic pregnancy is very low, particularly in implant contraceptive users. Despite this fact, little is known about mechanism of implant failure including its correlation to ectopic pregnancy, and studies are limited. This case report presented a levonorgestrel implant contraceptive failure result in ectopic pregnancy. A 21-years-old woman P1001 was provided with levonorgestrel implant seventh month before admission. Patient was presented to emergency department after suffering from severe lower abdominal pain. She was diagnosed with ruptured ectopic pregnancy and underwent exploratory laparotomy. Her ruptured right fallopian tube was ligated and partially removed. Histopathological examination supported the diagnosis chorionic villi lined with syncytiotrophoblast and cytotrophoblast cells in right fallopian tube tissue were found. The levonorgestrel implant was removed and she was scheduled for next contraceptive counseling. This case report emphasizes the fact that low incidence of contraceptive implant failure, does not rule out the possibility of ectopic pregnancy. Several hypotheses have been proposed as the cause of ectopic pregnancy. Further research is necessary to determine definitive etiology in ectopic pregnancy with levonorgestrel implant contraceptive failure.

KEYWORDS

Levonorgestrel implant, Implant failure, Ectopic pregnancy, Case report,



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INTRODUCTION

Implant contraception is a long-acting reversible contraception (LARC) that has 99.95% effectiveness and lasts for 3-5 years. Implant contraceptive placed subdermally on left upper arm.(1)(2)(3) There are 2 types of implant which are most frequently used, Etonogestrel (ENG) implant and Levonorgestrel (LNG) implant.(1,3) Primary mechanism of all subdermal implants are suppressing the mid-cycle escalation of luteinizing hormone (LH).(3) Ovulation will be suppressed 8 hours after implant insertion, and continues up to 3-4 weeks after removal.(4,5) Implant also works to thickening of cervical mucus and alteration of endometrial lining.(3,6) Ectopic pregnancy is a potentially life-threatening condition that leads to maternal death, approximately 1/100 pregnancies are ectopic. Ectopic pregnancy is defined as implantation of an embryo outside the uterine cavity. The most common site of implantation occurs in the ampulla of the fallopian tube, though implantation may also occur on the cornual, interstitium, ovary, cervix, abdominal wall, bowel, or within a cesarean section scar.(7) Although implant has superior effectiveness, there have been reported cases that indicate implant failure. This article reported an implant contraceptive failure resulted in unintended pregnancy, in this case an ectopic pregnancy.

A 21-year-old unmarried woman P1001 presented to the emergency department for a complaint of abdominal pain that started 9 days and worsened one day prior to admission. She had her last menstrual period 5 weeks 6 days prior to presentation. Her abdominal pain was not followed by vaginal bleeding. The history of pelvic inflammatory disease, surgery or ectopic pregnancy earlier was denied. Her first baby was born with spontaneously vaginal delivery. The patient was provided with a LNG implant at a public health center on November 2022, one month after delivering her first born baby. Two rods of LNG implant had been inserted on the $\frac{1}{3}$ distal left antebrachial, subdermally by midwife. Patient had a regular menstrual period with 28 days cycle and 5-7 days of duration. She had never been on long-term medication related to any disease. On investigation, her blood pressure was 100/60 mmHg, heart rate 110 beats/min, respiratory rate 16x/min and 36.5°C of axilla of temperature. Her body mass index (BMI) was 27.99 kg/m². Her abdomen was distended with lower right quadrant tenderness, positive muscular defense and normal bowel sound. Slinger pain found positive on vaginal touche. Per speculum a healthy normal cervix without vaginal bleeding was seen. Her laboratorium result showed markedly positive urine pregnancy and Hemoglobin (Hb) 10g/dL. Transabdominal sonography found anteflexion uterus with Complex Mass (CM) around the pouch of Douglas (Figure 1). Ruptured ectopic pregnancy as a provisional diagnosis was made and underwent exploratory laparotomy.



Figure 1. Anteflexion uterus with complex mass (CM) in the pouch of Douglass

Intra-operative, 600mL of blood clot and 400mL of hemoperitoneum was evacuated. An ampullary rupture within right fallopian tube was visualized which blood was oozing. (Figure 2) It decided to underwent right tubal ligation and artial salphingectomy. Bilateral ovarian, left fallopian tube and uterus were normal. Her LNG implant was removed (Figure 3).

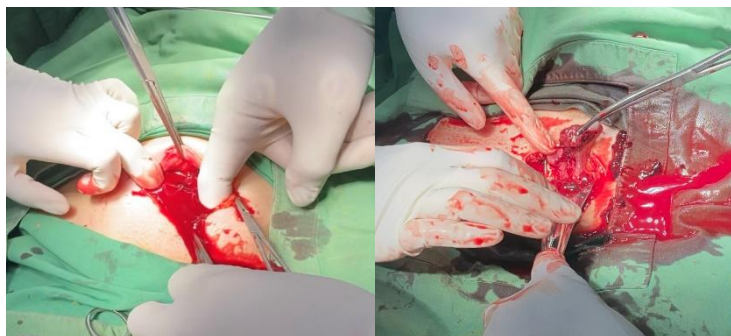


Figure 2. Hemoperitonium (right); ruptured ampullary tubal (left)

She had uneventful post-operative care and her Hb was 9.6g/dL. Her right fallopian tube (Figure 3) was sent to histopathological examination.

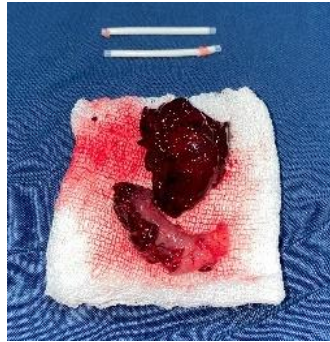


Figure 3. Two LNG Rods; Blood Clot; Right fallopian tube tissue

Histopathology examination found necrotic areas with decidua basalis cells and chorionic villi lined with syncytiotrophoblast and cytotrophoblast cells (Figure 4). She was then scheduled for next contraception counseling.

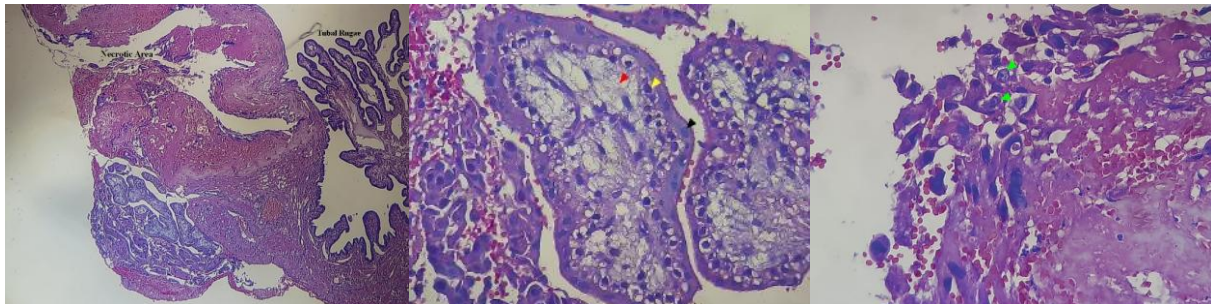


Figure 4. Necrotic area and Tubal Rugae (right); chorionic villi (red arrow); cytotrophoblast cell (yellow arrow); syncytiotrophoblast cell (black arrow); decidua cell (green arrow)

RESEARCH METHOD

This article reports an incidence of ruptured ectopic pregnancy in patient with levonorgestrel implant. This case was identified in early 2024 at Garbamed Hospital, Bali. This case emphasizes the possibility ectopic pregnancy influenced by levonorgestrel implant. In this article also present several literature obtained from several sources including Pubmed, Ebsco, Medline, Science Direct, Cochrane published by the last decade.

RESULT AND DISCUSSIONS

Case Discussion

Implant brands vary from Norplant®, Implanon®, Sino-implant®, Jadena®, Indoplant® etc. In Indonesia, the majority implant are free provided by the Badan Koordinasi Keluarga Berencana Nasional (BKKBN) which contain 2 rods of implant with 75 mg LNG each rod.¹

Levonorgestrel, is a second-generation of synthetic progestin and gonane derivative. It has been used widely as an active compound in contraceptive, specially hormonal implants.(8,9)LNG binds to progesterone and androgen receptors and cause inhibition of secretion of gonadotropin-releasing hormone (GnRH) from hypothalamus. As the result ovulation will be inhibited by prevent the luteinizing hormone surge that occurs on pre-ovulation stage.(10,11)Levonorgestrel also works to thickening cervical mucus, alteration of endometrial lining and reduction of ciliary beat frequency (CBF).(3,12)

Levonorgestrel implants slowly released into circulation. LNG implants could last up to 3-5 years. LNG levels in circulation will increase directly in the first month after placement and slowly decrease by time.(13–15)Peak concentration LNG in plasma also depends on the release rate of the implant, which may differ between brands. LNG implant bioavailability estimated about 66% in circulation.(15)LNG undergo metabolism in the liver through CYP3A4 before it excreted in urine.(11)

The risks of ectopic pregnancy are higher in women who smoke or have history of damaged fallopian tubes due to pelvic infections, surgery, or previous ectopic pregnancy.(16)Ectopic pregnancies would resolve by spontaneous resolution or with medical therapy, but others continue to grow and can lead to rupture of the tube. Some cases of ectopic pregnancy need to perform procedural treatment or surgery.(17)Latest evidence supports the hypothesis of tubal ectopic pregnancy is caused by a retention of the embryo within Fallopian tube due to interrupted embryo-tubal transport and remodeling tubal environment allowing early implantation to occur.(18)

The classic triad symptoms of an ectopic pregnancy include vaginal bleeding, lower abdominal pain and amenorrhea or a positive urinary pregnancy test.(19)On physical examination, signs of hemodynamic instability and hemoperitoneum can be found in women with ruptured ectopic pregnancy, while in patient with unruptured ectopic pregnancy often have slinger pain and adnexal tenderness.(20)In this case, patient was having severe abdominal pain with positive urinary pregnancy test. She had hemodynamic instability because of a ruptured ectopic pregnancy and bleeding in peritoneum.

Despite the rate of implant failure being very low (<1%), it does not prevent pregnancy. A study reported failure of implant in obese women 0.23 per 100 women-year.(21,22) Whereas the incidence of ectopic pregnancy ranged from 0 - 2.9 per 1000 women-year.(23)Another study also reported a case of ectopic pregnancy with a history of Implanon® insertion.(24)

Up to now, the mechanisms of implant failure are paradoxical. Several hypotheses have been proposed, but very uncommon cases of unintended pregnancy and ectopic pregnancy as the effect of implant failure made it difficult to

study. Besides, each brand of implant produced different drug release rate, which made different dose to inhibit LH escalation.(13)

Need to be concerned about drug-drug interactions between LNG with other drugs in plasma, including its metabolism in the liver. Some drugs were reported could induce CYP3A4 activity in the liver such as anticonvulsants, carbamazepine, phenytoin, barbiturate, St. John's wort, rifampicin, reverse transcriptase inhibitor, pioglitazone and glucocorticoids. Increased CYP3A4 activity believed to reduce LNG bioavailability and efficacy.(14,25)High activity of CYP3A4 increasing LNG clearance, caused by higher of hepatic degradation.(26)Low LNG bioavailability and concentration in serum/plasma below the threshold, leading to loss of contraceptive effect to inhibit ovulation.

In this case, the history of long-term medicine used was denied by the patient. Nevertheless, the patient's BMI was overweight. A higher BMI has an inverse correlation with LNG concentration in circulation.(13)It suggesting an increases BMI might decrease LNG in serum/plasma.

In addition, LNG could down regulate the expression of transient receptor potential vanilloid (TRPV) 4 channels. TRPV4 is located in the human reproductive tract which generates of Ca^{2+} influx to induce CBF. Downregulation TRPV 4 by LNG could limiting Ca^{2+} influx, causes CBF reduction and result in embryonal retention in Fallopian tube.(12)Embryonal retention in Fallopian tube potentially lead to ectopic pregnancy.(18)

Several hypotheses were proposed, but did not support as a definitive risk factor for this patient. The only overweight BMI suspected as risk factor for LNG implant failure, whereas there was no absolute risk for ectopic pregnancy in this patient. The mechanism LNG reducing tubal motility results in ectopic pregnancy could hold responsible, but it can only be postulated. This case highlights the need for further research regarding the influence of BMI on implant contraceptive, mainly with LNG compound. Further evidence is also needed regarding the mechanism of LNG whether oral or implant prepare reduces CBF in the fallopian tube.

CONCLUSION

Ectopic pregnancy can occur unexpectedly, with patients often unaware of their condition until symptoms of rupture appear. Although contraceptive implant failure is rare, it does not eliminate the risk of pregnancy, including ectopic pregnancy. This case report highlights an instance of ectopic pregnancy following levonorgestrel (LNG) implant contraceptive failure. To better understand this risk, future research should focus on identifying potential direct causes linking LNG implant failure to the incidence of ectopic pregnancy.

REFERENCE

1. BKKBN. Pedoman Pelayanan Kontrasepsi dan Keluarga Berencana. 1st ed. Vol. 1. Jakarta: Direktorat Kesehatan Keluarga Kementerian Kesehatan Republik Indonesia; 2020. 33–34 p.
2. Beasley A, Schutt-Ainé A. Contraceptive procedures. *Obstet Gynecol Clin North Am.* 2013;40(4):697–729.
3. Espey E, Hofler L. Long-Acting Reversible Contraception : Implants and Intrauterine Devices. *Obstetrics & Gynecology.* 2017;130(121):251–69.
4. Coelingh Bennink HJT. The pharmacokinetics and pharmacodynamics of Implanon®, a single-rod etonogestrel contraceptive implant. *European Journal of Contraception and Reproductive Health Care.* 2000;5(SUPPL. 2):12–20.
5. Schreiber CA, Barnhart K. Contraception. Eighth Edi. Yen & Jaffe's Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management: Eighth Edition. Elsevier Inc.; 2019. 962-978.e4 p.
6. Croxatto HB. Mechanisms that explain the contraceptive action of progestin implants for women. *Contraception.* 2002;65(1):21–7.
7. Panelli DM, Phillips CH, Brady PC. Incidence, diagnosis and management of tubal and nontubal ectopic pregnancies: a review. *Fertil Res Pract.* 2015;1(1):1–20.
8. Cunningham FG, Leveno KJ, Bloom SL, Dashe JS, Hofman BL, Casey BM, et al. Williams OBSTETRICS. 25th ed. New York: McGraw-Hill Education; 2018.
9. Strauss, Jerome F, Barbieri Robert L GAR. Yen & Jaffe's Reproductive Endocrinology Physiology, Pathophysiology, and Clinical Management. 8th ed. Philadelphia: Elsevier Inc; 2019.
10. Kahlenborn C, Peck R, Severs WB. Mechanism of action of levonorgestrel emergency contraception. *Linacre Quarterly.* 2015;82(1):18–33.
11. Stanczyk FZ, Roy S. Metabolism of levonorgestrel, norethindrone, and structurally related contraceptive steroids. *Contraception.* 1990;42(1):67–96.
12. Li C, Wu YT, Zhu Q, Zhang HY, Huang Z, Zhang D, et al. TRPV4 is involved in levonorgestrel-induced reduction in oviduct ciliary beating. *Journal of Pathology.* 2019;248(1):77–87.
13. Hofmann BM, Apter D, Bitzer J, Reinecke I, Serrani M, Höchel J, et al. Comparative pharmacokinetic analysis of levonorgestrel-releasing intrauterine systems and levonorgestrel-containing contraceptives with oral or subdermal administration route. *European Journal of Contraception and Reproductive Health Care.* 2020;25(6):417–26.

14. Karthik Lingineni, Ayyappa Chaturvedula, Brian Cicali, Rodrigo Cristofolletti, Thomas Wendl, Joachim Hoechel, Joshua D. Brown, Valvanera Vozmediano SS. Determining the Exposure Threshold for Levonorgestrel Efficacy Using an Integrated Model Based Meta-Analysis Approach. *Clinical Pharmacology and Therapeutics*. 2021;111:509–18.
15. Kim S, Cicali B, Pressly M, Da Silva L, Wendl T, Vozmediano V, et al. Model-Based Analysis of In Vivo Release Data of Levonorgestrel Implants: Projecting Long-Term Systemic Exposure. *Pharmaceutics*. 2023;15(5).
16. Kumar Vi, Gupta J. Tubal ectopic pregnancy Pregnancy and childbirth Tubal ectopic pregnancy. *BMJ Clin Evid*. 2012;02(1406):1–29.
17. Po L, Thomas J, Mills K, Zakhari A, Tulandi T, Shuman M, et al. Guideline No. 414: Management of Pregnancy of Unknown Location and Tubal and Nontubal Ectopic Pregnancies. *Journal of Obstetrics and Gynaecology Canada*. 2021;43(5):614-630.e1.
18. Kopp-Kallner H, Linder M, Cesta CE, Segovia Chacón S, Kieler H, Graner S. Method of Hormonal Contraception and Protective Effects Against Ectopic Pregnancy. *Obstetrics and gynecology*. 2022;139(5):764–70.
19. Ranji GG, Usha Rani G, Varshini S. Ectopic Pregnancy: Risk Factors, Clinical Presentation and Management. *Journal of Obstetrics and Gynecology of India*. 2018;68(6):487–92.
20. Mackay S, Layden E, Madhra M. Ectopic pregnancy. *Obstet Gynaecol Reprod Med*. 2023;33(3):81–7.
21. Frieden TR, Jaffe HW, Cono J. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Vol. 65, Centers for Disease Control and Prevention. 2016.
22. Xu H, Wade JA, Peipert JF, Zhao Q, Madden T, Secura GM. Contraceptive failure rates of etonogestrel subdermal implants in overweight and obese women. *Obstetrics and Gynecology*. 2012;120(1):21–6.
23. Callahan R, Yacobson I, Halpern V, Nanda K. Ectopic pregnancy with use of progestin-only injectables and contraceptive implants: A systematic review. *Contraception*. 2015;92(6):514–22.
24. Bouquier J, Fulda V, Bats AS, Lécuru F, Huchon C. A life-threatening ectopic pregnancy with etonogestrel implant. *Contraception*. 2012;85(2):215–7.
25. Sunaga T, Cicali B, Schmidt S, Brown J. Comparison of contraceptive failures associated with CYP3A4-inducing drug-drug interactions by route of hormonal contraceptive in an adverse event reporting system. *Contraception*. 2021;103(4):222–4.

26. Zhang N, Shon J, Kim MJ, Yu C, Zhang L, Huang SM, et al. Role of CYP3A in Oral Contraceptives Clearance. Clin Transl Sci. 2018;11(3):251–60.