

## Ectopic Pregnancy Following Levonorgesterol-Only Emergency Contraception: The First Malaysian Case Report

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### ABSTRAK

*Levonorgestrel (LNG) sememangnya dikenali sebagai pil pencegahan kehamilan kecemasan (EC) yang selamat and berkesan. Namun begitu, kes kehamilan luar rahim akibat daripada kegagalan LNG EC pernah dilaporkan. Insiden kehamilan luar rahim yang tepat sukar ditentukan akibat kemudahan untuk mendapatkan LNG EC daripada farmasi tanpa preskripsi. Kami melaporkan satu kes kehamilan luar rahim seorang pesakit perempuan tidak berkahwin yang berumur 18 tahun. Beliau telah mengambil LNG EC dalam jangkamasa 48 jam selepas persetubuhan. Beliau dihantar ke jabatan kecemasan pada minggu kelapan tempoh hamil dengan abdomen akut dan renjatan hipovolemik. Pembedahan laparotomi mengesahkan kehamilan di luar rahim yang sudah pecah di bahagian tiub fallopio dan salpingektomi telah dilaksanakan. Pesakit tersebut dibenarkan pulang selepas dua hari. Kami ingin menekankan kesan sampingan dan membincangkan perkaitan kehamilan luar rahim selepas penggunaan LNG EC.*

*Kata kunci: Levonorgestrel, pil pencegahan kehamilan kecemasan, kehamilan luar rahim*

### ABSTRACT

Levonorgestrel (LNG) is a well-known safe and efficacious emergency contraception (EC). However, ectopic pregnancy following the failure of LNG-only EC has been reported. The exact incidence of ectopic pregnancy has been hindered by lack of data due to the fact that LNG-only EC is accessible at pharmacies without a prescription. We describe a case of ectopic pregnancy in an 18 year-old single woman who took LNG-only EC within 48 hours of unprotected sexual intercourse.

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She presented to the emergency department at 8 weeks period of amenorrhoea with an acute abdomen and hypovolaemic shock. Laparotomy confirmed a ruptured right tubal pregnancy and salpingectomy was performed. The patient was discharged well after 2 days. We aim to highlight this potential adverse effect and to discuss the plausible causality of ectopic pregnancy following administration of LNG-only EC.

Key words: Levonogestrel, emergency contraception, ectopic pregnancy

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## INTRODUCTION

Emergency contraception (EC) is defined as any drug or device used as an emergency measure to prevent an unplanned pregnancy after unprotected sexual intercourse or a known contraceptive failure (Cheng et al. 2004; Gemzell-Danielsson 2010). Currently, Levonorgestrel-only EC is recognized as a well-established EC (Gemzell-Danielsson 2010). 1.5 mg Levonorgestrel (LNG) should be administered within 72 hours after an unprotected sexual intercourse, either in a single dose or in two doses of 0.75 mg 12 hours apart (Cheng et al. 2004). The effectiveness of LNG as EC had been estimated to be between 57-95% depending on the delay of administration, highest when administered within 24 hours (Mikolajczyk & Stanford 2007; Gemzell-Danielsson 2010; Kozinszky et al. 2011). However, the risk of ectopic pregnancy should be considered following LNG-only EC failure. Numerous cases of ectopic pregnancy after the use of LNG-only EC had been previously reported (Sheffer-Mimouni et al. 2003; Ghosh et al. 2009; Kozinszky et al. 2011). There was a rate of 4.1% ectopic pregnancies following failure of LNG-only EC, which was higher than the incidence of 1.1% to 1.6% in spontaneous pregnancies

(Varma & Gupta 2009; Gainer et al. 2001).

## CASE REPORT

A healthy 18-year-old sexually active nulliparous woman presented to the emergency department with sudden onset of generalised abdominal pain associated with symptoms of severe anaemia at eight weeks period of amenorrhoea. Her menses were regular at 28 to 30 days per cycle. Urine pregnancy test was positive. She had no known risk factor for ectopic pregnancy. She did not practice any method of contraception. She provided a history of unprotected sexual intercourse approximately two weeks after her last normal menstrual period. Following the unprotected sexual intercourse, she took a course of LNG-only EC, 2 doses of 0.75 mg 12 hours apart, with the first dose being administered within 48 hours. The LNG-only EC was purchased over the counter at a local pharmacy. She did not have any sexual intercourse consequently.

On assessment, she was in Stage III of hypovolaemic shock with severe pallor. Her blood pressure was 84/39 mmHg and pulse 97/min. Abdomen was distended and guarded. Bimanual

examination revealed a uterus of 6 weeks size with boggy at the pouch of Douglas. Transvaginal ultrasonography revealed an empty uterus with presence of large amounts of haemoperitoneum. She underwent a laparotomy and was found to have a ruptured right tubal pregnancy at the isthmus and a massive haemoperitoneum of 3000 ml. The left tube was normal. A right salpingectomy was performed. She was transfused with three pints of packed cells. The postoperative period was uneventful and she was discharged two days later with a haemoglobin level of 10.5 g/dL. Histology of the surgical specimen confirmed a tubal pregnancy.

## DISCUSSION

The risk factors of tubal ectopic pregnancies include previous ectopic pregnancy, pelvic inflammatory disease, history of pelvic or tubal surgery, intrauterine contraceptive device use, salpingitis isthmica nodosa, infertility, smoking and assisted conception, although up to half of the women with ectopic pregnancies did not have any identifiable risk (Varma & Gupta 2009; Marion & Meeks 2012). However, the failure of emergency LNG-only EC had not been established as a risk factor for tubal ectopic pregnancy despite reported increased rate of ectopic pregnancy following its failure.

The mechanism of action of LNG-only EC is not fully known but studies had shown that the mechanism of action and efficacy vary with phase of the menstrual cycle when the LNG EC was administered (Croxatto et al. 2003; Ghosh et al. 2009). The administration

of LNG prior to the LH surge was able to inhibit or delay the LH surge, delay follicular development and arrest the unruptured follicles (Croxatto et al. 2003; Gemzell-Danielsson 2010). Administration of LNG also transiently increased the viscosity of cervical mucus, which inhibited the passage of sperms (Noe et al. 2011). However, if taken when LH surge had already started, LNG is not able to prevent ovulation and hence, may be the cause for the reported failures using LNG EC (Croxatto et al. 2004). In addition, the administration of LNG during the peri- and postovulatory periods does not confer any significant change in the endometrial histology or any studied markers of receptivity during the mid-luteal phase at the expected time of endometrial receptivity and implantation (Ghosh et al. 2009; Gemzell-Danielsson 2010). It was concluded that LNG-only EC was highly effective in preventing pregnancy if administered prior to ovulation but if administered after ovulation, it was ineffective in preventing pregnancy, as it did not have any effect on the subsequent reproductive processes, including the implantation of the embryo (Noe et al. 2011).

Numerous studies had shown that the single dose of 1.5mg of LNG was equally as efficacious as two doses of 0.75mg LNG as a mode of emergency contraception. In a review of emergency contraception, there was no evidence to indicate any difference in the rates of ectopic pregnancy between these two regimens (Cheng, et al. 2004).

Smooth muscle contraction and ciliary activity of the fallopian tube

played an important role in the embryo-tubal transport, should fertilisation occur (Shaw et al. 2010). High levels of progesterone in the early luteal phase had been shown to reduce or slow ciliary activity in the fallopian tube and affect the embryo-tubal transport (Paltieli et al. 2000; Gemzell-Danielsson 2010). Following the administration of two doses of 0.75 mg LNG at 12 hours apart or a single dose of 1.5 mg of LNG, the serum level of LNG was high, reaching maximum levels of 25.3 nmol/L and 39.3 nmol/L respectively (Johansson et al. 2002). Theoretically, high levels of LNG would affect the motility of the tubes (Sheffer-Mimouni et al. 2003). LNG was capable of markedly inhibiting the muscular contraction of the fallopian tube based on an in-vitro study (Wanggren et al. 2008). The effect of LNG on the ciliary function and tubal muscular contraction could be the plausible explanation for the occurrence of ectopic pregnancy following emergency contraceptive failure.

There were three case reports on the failure of LNG-only EC administered during mid-cycle resulting in tubal ectopic pregnancies (Sheffer-Mimouni et al. 2003; Ghosh et al. 2009; Kozinszky et al. 2011). Camp et al. (2003) reported a rate of 7.4% (n = 21) of ectopic pregnancies from 285 pregnancies after the failure of LNG EC, while Gainer et al. (2001) reported a rate of 4.1% (n = 3) from a total of 73 pregnancies resulting from product failures (Camp et al. 2003; Gainer et al. 2001). However, there was no valid or unbiased assessment done and the authors did not rule out the possibility of unreported normal

pregnancies following the product failure (Camp et al. 2003). A systematic review had shown that the rate of ectopic pregnancy following failure of LNG-only EC did not exceed the rate observed in spontaneous pregnancies as EC was effective in reducing risk of unwanted pregnancy and in turn, preventing ectopic pregnancy (Cleland et al. 2010). Nevertheless, the occurrence of ectopic pregnancy following the failure of LNG EC should not be disregarded. In comparison with the intrauterine device (IUD), a meta-analysis of case-control studies reported that there is no increased risk of ectopic pregnancy with IUD use but a pregnancy with IUD in-situ is more likely to be an ectopic pregnancy. (Xiong et al. 1995).

## CONCLUSION

This case report aims to highlight the occurrence of ectopic pregnancy following the failure of LNG-only EC despite being administered correctly. This is the first case being reported in Malaysia. Numerous case reports and literature had reported ectopic pregnancies after the use of LNG-only EC but it had not been statistically proven to be an established risk factor. This may be due to absence of an accurate method or research to report the exact incidence. However, as recent systematic reviews have failed to prove an increased risk of ectopic pregnancy following LNG-only EC compared to spontaneous conception, the public must not be misled into believing that there is an increased risk of ectopic pregnancy until there

is sufficient literature evidence. This is to avoid unnecessary fear to the usage of LNG-only EC causing a rise in occurrence of unwanted pregnancies and baby abandonment which had been a disconcerting phenomenon in Malaysia recently.

Regulatory bodies in the UK, New Zealand and other countries have made recommendations to “consider the possibility” of ectopic pregnancy following the failure of LNG-only EC (Cleland et al. 2010). Therefore, both physicians and the public should be made aware of this adverse effect of LNG-only EC use. Prescription leaflets should contain information regarding ectopic pregnancy being one of the side effects of LNG EC use. In addition, physicians and pharmacists who prescribe the EC should educate the users to seek early consultation should there be presence of amenorrhoea for urine pregnancy test, menstrual abnormalities or abdominal pain following the administration.

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