Indian Journal of Obstetrics and Gynecology
Volume 1 Number 1, January - June 2013

Sirenomelia in a Fetus Conceived after Levonorgestrel Emergency Contraception Failure: A Case Report and Review of Literature

Garima Kachhawa, Sunesh Kumar, Vaishali Suri, M Goyal

Abstract

Use of levonorgestrel as emergency contraception is a safe and effective measure to prevent unwanted pregnancy. Limited data have been available on the effect of the pregnancy outcomes and there have been no reports on adverse birth outcomes, but only a small number of normal deliveries after levonorgestrel emergency contraception (LNG–EC) failure have actually been documented. We present a case of pregnancy following failure of levonorgestrel emergency contraception. The pregnancy was terminated as the fetus was affected by a lethal condition, sirenomelia or mermaid syndrome. Although LNG–EC taken during the conception cycle has no significant effects on the incidence of malformation, however the number of investigated pregnancies is relatively small, and these findings need to be further assessed in the context of larger groups including those are that are chosen to be aborted.

Keyword: *Levonorgestrel; Emergency contraception failure; Sirenomelia; LNG-EC.*

Department of Obstetrics and Gynaecology
All India Institute of Medical Sciences, New Delhi, India
Garima Kachhawa, Assi. Professor.

Department of Obstetrics and Gynaecology
All India Institute of Medical Sciences, New Delhi, India
Sunesh Kumar

Department of Pathology
All India Institute of Medical Sciences, New Delhi, India
Vaishali Suri

Department of Obstetrics and Gynaecology
All India Institute of Medical Sciences, New Delhi, India
M Goyal

Correspondence to:
Dr Garima Kachhawa

Received on 04 Feb, 2013

Accepted on 27 Feb, 2013

Introduction

Levonorgestrel emergency contraception (LNG- EC) is effective in reducing the risk of unintended pregnancy from a single mid-cycle act of unprotected intercourse from 8% to 1.1% [1] At a dose of 1.5 mg (given either as a single 1.5 mg dose or two 0.75 mg doses taken 12 h apart), it is safe, well-tolerated and is not associated with increased risk of major congenital anomalies [2,3]. In the context of LNG–EC failure, only limited data have been available on the effect of the pregnancy outcomes and there have been no reports on adverse birth outcomes, but only a small number of normal deliveries after LNG–EC failure have actually been documented [4,5]. There are a few sporadic reports of congenital malformations in LNG-EC exposed fetuses like polycystic kidney disease, hip dislocation, cleft palate or facial hemangioma [6]. We report a case of a pregnancy continued after failure of LNG-EC and fetus with clinical features of sirenomelia including fused lower limbs with medial position, bilateral renal agenesis, and a single large umbilical artery. The pregnancy was terminated on the basis of ultrasound diagnosis of bilateral renal agenesis with absent liquor. Recent literature describing the etiology of sirenomelia and any association if any with the LNG-EC is reviewed.

Case report

A 24 year old married woman came to our outpatient department with a history of a positive pregnancy test after failure of LNG-EC in periconception period. She gave history of unprotected intercourse approximately 10 days after her last menstrual period and took two doses of 750 mcg of LNG, 12 h apart within 12 hours of intercourse. There was no history of repeat unprotected intercourse, further in

the same cycle. Her menstrual periods were overdue by 18 days and a transvaginal sonogram revealed a single gestation sac in uterus with a live fetus of around 7 weeks + 3 days. The couple decided to continue the pregnancy. She was in good general health with no long-term medical problems and was prescribed folic acid supplementation. Routine antenatal investigations namely complete haemogram, fasting blood glucose; thyroid function tests as per our institute protocol were all within normal limits. There was no family history of diabetes or any genetic disorder. Her antenatal course was uneventful until anomaly scan at 16 wks revealed a single live pregnancy of 16+2 weeks with severe oligohydramnios, bilateral renal agenesis and single umbilical artery. The couple after counseling with geneticist and obstetricians, decided to go for medical termination of pregnancy. After completing informed consent procedure, the patient was induced with tab. Misoprostol 400 mg inserted vaginally and repeated after 4 hours. After 8 hours of uterine contractions, patient aborted a fetus weighing 150 gms, of undetermined sex and with features of mermaid syndrome [Figure -1(a,b)]. On gross examination, the fetus had only one fused lower limb, upper limb was also malformed with syndactyly. External genitalia and anal opening could not be visualized. The fetus was sent for autopsy and cytogenetic study. The karyotype was 46XY and histopathology report showed that all thoracic organs were within normal limits except lungs which were hypoplastic. Bilateral kidney, uterus and bladder were absent and the intestine ended bluntly. Only one gonad was identified in the abdomen on the left side which showed features of testicular parenchyma. The umbilical cord showed two vessels. The patient was discharged in a healthy condition and OGTT with 100 gms of glucose done 6 months after delivery was within normal limits.

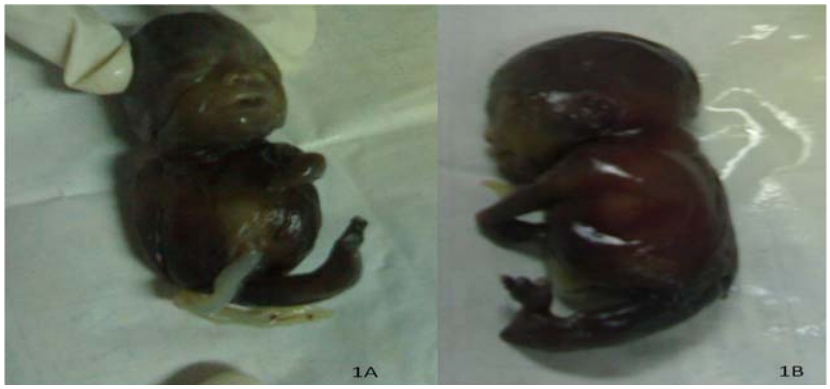
Discussion

Caudal regression syndrome (CRS; including sirenomelia) is a rare congenital condition characterized by varying degree of developmental failure ranging from a partial sacral agenesis to the absence of lumbosarcal spine, hypoplasia, or fusion of the lower extremities and visceral anomalies [7]. In the mst severe cases, the lower limbs are fused, also known as sirenomelia or mermaid syndrome. Sirenomelia is a very rare congenital malformation, with an incidence of between 1:60,000 and 1: 100,000 [8]. It is characterized by a single or fused lower limbs associated with other severe anomalies such as bilateral renal agenesis, which are incompatible with life in majority of cases [8]. The etiology of sirenomelia is widely debated and there is no consensus as to the autonomic status of sirenomelia versus CRS.

However, there is evidence suggesting that CRS and sirenomelia are different. The latter is supposedly the result of an early vascular aberration leading to a ''vitelline artery steal'' [7], whereas CRS is a heterogenous disorder in as much as the etiology and pathology are concerned. About 15–25% of mothers of children with caudal regression syndrome have diabetes mellitus [7]. Nevertheless, recent advances in the understanding of axial mesoderm patterning during early embryonic development suggest that sirenomelia represents the most severe form of CRS [10].

Bohring et al postulate that the spectrum of malformations observed in caudal regression syndrome and sirenomilia represents abnormalities in blastogenesis, and is due to disturbances in primary embryonic field [11]. The entire embryo during blastogenesis (days 1 to 28) represents the primary field thus suggesting that such defects are caused by disruption of caudal mesoderm during early development [9]. It is generally believed that LNG can prevent or delay ovulation, modify endometrial receptivity and impair the formation of the corpus luteum [12]. The mechanism of action and effectiveness vary with the phase in menstrual cycle when administered. It is probably most effective in the follicular phase, when it interferes with the ovulatory process by inhibiting the luteinizing hormone (LH) surge [13]. When LNG is administered after the onset of the LH surge,

Figure 1a: Anterior view & Figure 1b: Lateral view



it appears to have no effect on the ovulatory process, and this may explain the reported failures of this EC method. It seems prudent to think that in cycle where LNG fails to prevent ovulation but can still affect endometrial receptivity, modifies vascularity affecting implantation and blastogenesis [14].

Animal experiments have shown that CRS-like syndrome could be induced by agents including retinoic acid, diethylpropion, lithium, sulfamide, cadmium, lead, ochratoxin A, vitamin A deficiency, radiation, hyperthermia, organic fat solvents, and 6-aminonicotinamide. Familial occurrence of CRS has been reported, but no Mendelian pattern of inheritance has been established [15]. The exact etiology and pathogenetic mechanisms are poorly understood, but maternal diabetes, genetic predisposition, and vascular hypoperfusion have been proposed [7]. Our patient was non diabetic and had no family history in particular of diabetes mellitus or any genetic disorder.

Because of the rarity of pregnancies in those using levonorgestrel and the little research conducted in this area, the potential for developmental toxicity has not been rigorously evaluated. When LNG–EC fails, some nulliparous women choose to continue their pregnancies. In a retrospective analysis of women exposed to levonorgestrel with particular interest in the potential teratogenic risks after prenatal levonorgestrel exposure, De Santis et al and more recently Zhang et al found no difference in the rates of congenital or genital anomalies compared with a control group and the baseline risk expected [6,16]. A possible association between antenatal exposure to progestins and hypospadia and other urinary tract anomalies already has been with the long term use of levonorgestrel rather than with the short-term, low-dosage preparations used in the emergency contraception [17].

A recent experimental study looked at the role of retinoic acid in producing CRS in the mouse fetus. Retinoic acid, when given in variable dosages to mouse fetuses, resulted in CRS in most of the survivors. This study showed a combination of cell death, vascular disruption, and tissue deficiency as the highlight of caudal regression. Low doses produced caudal regression, while high doses resulted in caudal agenesis [18]. The LNG-EC has an antiproliferative effects on the endometrium, which becomes atrophic and unresponsive to estrogens. It has been recently suggested that defects in formation of the primitive streak during the late gastrula stage could lead to caudal body malformations including part of the urogenital or reproductive organs as well as the hind limbs [10].

The involvement of non-gonadal and locally produced masculine factors (or "effector molecules") which can potentially interact with hormonal signaling in the sexually developing organs has not yet been elucidated but suggested [20, 21] In another case, a possible drug-related etiology for extreme caudal agenesis in a human fetus has been suggested [23]. The mother had used minoxidil solution for hair loss 4 years prior to and during

gestation. She also received trimethoprim-sulfamethoxazole during the 1st trimester for an upper respiratory problem. There was no history of maternal diabetes or familial genetic diseases. Some animal studies have indicated a dose-dependent virilization of female fetuses related to LNG's androgenic character [24]. But others consider that there is not enough evidence to prove the relationship between the oral contraception pills and the pudendum abnormalities [25].

All of these studies and reports strongly suggest the teratogenic role of various chemicals in the genesis of sirenomelia and CRS. Majority of LNG – EC exposed pregnancies are aborted subsequently making it impossible to observe full effect on pregnancy outcome. We believe that even these pregnancies chosen to be terminated should be thoroughly evaluated antenatally and abortus should be examined in detail after termination.

Conclusion

The purpose of presenting this case is to add to the list of spontaneous reports, in the absence of any feasible mechanism of estimating exact incidence of this adverse effect. According to the best of our knowledge, this is the first case report of a fetus exposed to levonorgestrel and affected by sirenomelia, a severe form of CRS. LNG EC failure resulted in pregnancy in spite of using emergency pill in the correct phase of cycle (preovulatory). Although LNG–EC taken during the conception cycle had no significant effects on the incidence of malformation, however the number of investigated pregnancies is relatively small, and these findings need to be further assessed in the context of larger groups including those are that are chosen to be aborted.

There was no funding for this case report.

References

1. Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. Task Force on Postovulatory Methods of Fertility Regulation. *Lancet*. 1998; 8(352): 428-33.
2. Croxatto HB, Brache V, Pavez M, Cochon L, Forcelledo ML, Alvarez F, Massai R,Faundes A, Salvatierra AM. Pituitary-ovarian function following the standard levonorgestrel emergency contraceptive dose or a single 0.75-mg dose given on the days preceding ovulation. *Contraception*. 2004; 70: 442-50.
3. Sarkar NN. Levonorgestrel as an emergency contraceptive drug. *Int J Clin Pract*. 2003; 57: 824-8.
4. Cheng L, Gülmezoglu AM, Piaggio G, Ezcurra E, Van Look PF. Interventions for emergency contraception. *Cochrane Database Syst Rev*. 2008; 16(2): CD001324 .
5. Camp SL, Wilkerson DS, Raine TR. The benefits and risks of over-the-counter availability of Levonorgestrel emergency contraception. *Contraception.* 2003; 68: 309–17.
6. Zhang L, Chen J, WangY, Ren F, Yu W, Cheng L. Pregnancy outcome after levonorgestrel-only emergency contraception failure:a prospective cohort study. *Human Reproduction.* 2009; 24: 1605–11.
7. Krenova Z, Elstnerova L, Dolezel Z, Kren L. Caudal regression syndrome in one of dizygotic twins. *Fetal Pediatr Pathol*. 2010; 29: 419-23.
8. Stocker JT, Heifetz SA. Sirenomelia. A morphological study of 33 cases and review of the literature. *Perspect Pediatr Pathol*. 1987; 10: 7-50.
9. Stevenson RE, Jones KL, Phelan MC, Jones MC, Barr M Jr, Clericuzio C et al. Vascular steal: the pathogenetic mechanism producing sirenomelia and associated defects of the viscera and soft tissues. *Pediatrics*. 1986 ; 78: 451-7.
10. Valenzano M, Paoletti R, Rossi A, Farinini D, Garlaschi G, Fulcheri E. Sirenomelia pathological features, antenatal ultrasonographic clues, and a review of current embryogenic theories. *Human Reprod Update.* 1999; 5: 82–86.
11. Bohring A, Lewin SO, Reynolds JF, Voigtländer T, Rittinger O, Carey JC et al. Polytopic anomalies with agenesis of the lower vertebral column. *Am J Med Genet*. 1999; 19(87): 99-114.

12. Croxatto HB, Devoto L, Durand M, Ezcurra E, Larrea F, Nagle C, et al. Mechanism of action of hormonal preparations used for emergency contraception: a review of the literature. *Contraception.* 2001; 63: 111–21.
13. Marions L, Hultenby K, Lindell I, Sun X, Stabi B, Danielsson KG. Emergency contraception with mifepristone and levonorgestrel: mechanism of action. *Obstet Gynecol.* 2002; 100: 65–71.
14. Grant EC. Adverse reactions and emergency contraception. *Lancet*. 2001; 14(357): 1203.
15. Ross AJ, Ruiz-Perez V, Wang Y, Hagan DM, Scherer S, Lynch SA et al. A homeobox gene, HLXB9, is the major locus for dominantly inherited sacral agenesis. *Nat Genet*. 1998; 20: 358-61.
16. De Santis M, Cavaliere AF, Straface G, Carducci B, Caruso A. Failure of the emergency contraceptive levonorgestrel and the risk of adverse effects in pregnancy and on fetal development: an observational cohort study. *Fertil Steril.* 2005; 84: 296–99.
17. Beleza-Meireles A, Omrani D, Kockum I, Frisen L, Lagerstedt K, Nordenskjold A. Polymorphisms of estrogen receptor beta gene are associated with hypospadias. *J Endocrinol Invest*. 2006; 29: 5–10.
18. Padmanbhan R. Retinoic acid-induced caudal regression syndrome in the mouse fetus. *Reprod Toxicol.* 1998; 12: 496–98
19. Yamada G, Suzuki K, Haraguchi R, Miyagawa S, Satoh Y, Kamimura M et al. Molecular genetic cascades for external genitalia formation: an emerging organogenesis program. *Dev Dyn*. 2006; 235: 1738–52.
20. Yamada G, Satoh Y, Baskin LS, Cunha GR. Cellular and molecular mechanisms of development of the external genitalia. *Differentiation*. 2003; 71: 445–60.
21. Kallen B, Mastroiacovo P, Lancaster PA, Mutchinick O, KringelbachM, Martinez-Frias ML, et al. Oral contraceptives in the etiology of isolated hypospadias. *Contraception.* 1991; 44: 173– 82.
22. Zakin L, Reversade B, Kuroda H, Lyons KM, De Robertis EM. Sirenomelia in Bmp7 and Tsg compound mutant mice: requirement for Bmp signaling in the development of ventral posterior mesoderm. *Development*. 2005; 132: 2489–99.
23. Rojansky N, Fasouliotis SJ, Ariel I, Nadjari M. Extreme caudalagenesis. Possible drug-related etiology? *J Reprod Med.* 2002; 47: 241–45.
24. Hatcher RA, Nelson A. Combined hormonal contraceptive methods. In Contraceptive Technology, 19th edn. New York: Ardent Media, Inc: 2007, 391–460.
25. Mu¨ller AL, Llados CM, Croxatto HB. Postcoital treatment with levonorgestrel does not disrupt post fertilization events in the rat. *Contraception.* 2003; 67: 415–419.