Overdistended duplicated bladder and sudden fetal demise after inadvertent exposure to long-acting gonadotropin-releasing hormone agonist in early pregnancy

Erken gebelikte istenmeden meydana gelen uzun etkili gonadotropin salgılatıcını hormon agonisti maruziyeti sonucu oluşan aşın gerilmiş dublike mesane ve ani fetal ölüm

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Abstract

Gonadotropin-releasing hormone agonists are being increasingly used in infertility and gynaecological practice for treatment of fibroids, endometriosis and in vitro fertilization cycles. A 24-year-old nulliparous lady with a fibroid uterus had an inadvertent exposure to two doses of leuprolide acetate and conceived spontaneously while awaiting hysteroscopic myomectomy. The fetus suffered anomalies of urogenital system and sudden intrauterine fetal demise at 31 weeks gestation. Till date, no consensus has been gathered on the management of GnRHa. There is no concrete evidence in the literature that it causes fetal urogenital anomaly and demise. A 24-year-old nulliparous lady was referred to our institute with a diagnosis of fibroid uterus and severe dysmenorrhea. She had irregular menstrual cycles and underwent premenstrual endometrial aspiration and hysteroscopy at our centre, which revealed an anterior wall submucous myoma of size 4 cm x 4 cm, with a broad pedicle. Uterocervical length was 9 cm and rest of the cavity was normal. Endometrial histology revealed isthmic endometrium with few fragments of proliferative endometrium. She was planned for hysteroscopic myomectomy, and received two doses of leuprolide depot 3.75 mg monthly (first dose, 7 days after last menstrual period and the second dose a month later; did not menstruate but pregnancy test was negative) and was advised to use barrier contraception.

She followed with a positive urine pregnancy test at the next visit. Transvaginal ultrasound showed a single live fetus corresponding to 7 weeks and 3 days gestation. The couple was counseled regarding the possible teratogenic effects and they decided to continue with pregnancy. Triple screen at 16 weeks and level II scan at 19 weeks was normal with no structural defects. She was admitted once with localized pain and tenderness over the fibroid, at 27 weeks, but there were no features of degeneration. She received two doses of injection betamethasone 12 mg intramuscular, 24 hours apart, during her hospital stay and underwent a repeat ultrasound at 31 weeks due to decreased fetal movements, which showed bilateral mild fetal hydroureronephrosis and an overdistended duplicated urinary bladder (thick incomplete fundal septum) with a differential diagnosis of overdistended urinary bladder plus hydrometrocolpos (Fig 1). There was moderate oligohydramnios (amniotic fluid index 7 cm), with no other anomaly and normal Doppler flow parameters. Paediatric surgery evaluation was done. One week later, the patient was again admitted with decreased fetal movements and ultrasound done at this...
visit revealed intrauterine fetal demise. Her coagulation profile was normal and she was induced thrice with intracervical prostaglandin E2 gel 0.5 mg and delivered a male fetus weighing 1690 grams with grossly normal features. The couple refused an autopsy due to religious reasons. The etiology of duplicated urinary bladder is unknown. Duplication can be complete or partial, with complete duplication more common than incomplete duplication. Bladder development occurs during the fifth to seventh week of gestational development. Development depends upon many factors, such as proper mesenchymal differentiation, mesenchymal growth, urine production that stimulates bladder expansion, and detrusor contraction. Megacystitis, bladder duplication, and bladder septation are rare. Morbidity of these conditions is generally related to associated abnormalities (when present) such as high-grade vesicoureteral reflux or renal dysplasia. Only 50 reported cases of bladder duplication exist. There have been conflicting reports in literature regarding the safety profile and perinatal outcome of pregnancy after inadvertent exposure to GnRHa. Taskin et al. (1999) reported normal pregnancy outcome after inadvertent exposure to GnRHa. Lahat et al (2000). In the study group (n=6), one child had a major congenital malformation (cleft palate) and four children subsequently demonstrated neurodevelopmental abnormalities including epileptic disorder (n=1), attention deficit hypersensitivity disorder (n=3), motor difficulties (n=3) and speech difficulties (n=3). In the control group (n=20), one child had attention deficit hypersensitivity disorder (2). Till date, there is no clear answer concerning teratogenic and hormonal effects of GnRHa exposure in pregnancy. In our patient, the length of exposure must have been around 25 to 30 days, possibly till the stage of organogenesis leading to subtle effects on the developing fetus. Tan et al (2006) evaluated pregnancy outcomes in a group of infertile patients who conceived spontaneously while undergoing IVF with unrecognized daily exposure to GnRH a during the downregulation regime (3). Nine spontaneous pregnancies were recorded (0.43%). The median duration of inadvertent exposure to subcutaneous leuprolide acetate was 22 days. Seven pregnancies progressed to term and resulted in singleton live births with no apparent evidence of fetal abnormalities or aneuploidies. One pregnancy was complicated by parvovirus infection at 19 weeks gestation with transient fetal hydrops. Their experience reaffirms current evidence from earlier studies that accidental exposure to GnRH a in early pregnancy is safe. 35 pregnancies inadvertently conceived during the midluteal application of the long-acting gonadotropin-releasing hormone agonist triptorelin acetate before ovarian stimulation for in vitro fertilization have been already reported by Mayer et al. No increase in pregnancy wastage or appearance of congenital malformations occurred. Most of the conceptions occurred before the first or second IVF trial, and were associated with a significantly increased tendency to develop gestational diabetes (4).

To conclude, no consensus has been gathered on the management of GnRHa exposed pregnancies, the association is extremely weak and there is a need for further studies gathering many patients to draw any conclusions.

References