

In Utero Medroxyprogesterone Exposure After Contraceptive Failure

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Depo-Provera (depot medroxyprogesterone acetate, UpJohn) is a long-acting, injectable contraceptive drug that is administered as a 150-mg dose intramuscularly every 3 months.¹ Although its initial failure rate is only 0.3 per 100 women years,² the increasing use of injectable medroxyprogesterone will lead to increasing numbers of in utero exposures. The purpose of this paper is to describe a case in which injectable medroxyprogesterone failed to prevent conception and to review briefly the literature on in utero exposure to medroxyprogesterone.

Case Report

A 20-year-old woman came to the office 6 weeks after delivery of her first child for a routine examination and expressed interest in medroxyprogesterone injections. She had breast-fed for the first 4 weeks postpartum but had switched to formula with no complications. She was not taking any medications, did not smoke, and was not overweight. She had not previously used contraceptive hormones. As instructed, the patient returned at the beginning of her menses and was given an injection of 150 mg of medroxyprogesterone. She does not remember rubbing the injection area or experiencing any pain or bleeding. She returned in 86 days with no complications and was given her next injection.

After 2 weeks the patient became concerned that she had not menstruated and was informed by her physician that it was probably related to the medroxyprogesterone injections. One week later the patient called, stating that an over-the-counter urine pregnancy test was positive. A follow-up quantitative beta human chorionic gonadotropin (β -hCG) was 63,600 mIU/mL. On

bimanual examination the uterus was 10 to 12 weeks in size, and from the results of an obstetric sonogram, the fetal age was estimated to be 10 weeks. This dating indicates that conception occurred approximately 45 to 50 days after the initial injection. Another sonogram at 18 weeks showed normal development, and the rest of the pregnancy was uncomplicated. The patient gave birth to a 3720-g baby boy at 39 weeks' gestation (by first prenatal examination and 10-week sonogram, and confirmed by Dubowitz scoring system) with Apgar scores of 9 at 1 and 5 minutes. Findings on the neonatal examination were normal. The patient chose permanent sterilization, and she had a tubal ligation.

The case was reported to the World Wide Reporting Network of the Upjohn Company. Unfortunately the lot number of the Depo-Provera injected was not available; therefore, the manufacturer was unable to check for additional failures with that particular lot.

Discussion

Why did injectable medroxyprogesterone fail? What future contraception can be recommended to the patient? What are the possible short- and long-term side effects to the baby after in utero exposure to medroxyprogesterone?

Although the initial failure rate of injectable medroxyprogesterone is 0.3 per 100 women years, the rate increases to 0.9 per 100 women years by 36 to 70 months of contraception.² Some have speculated that injectable medroxyprogesterone could be less effective if the woman were extremely obese or if the injection were superficial or the site massaged, accelerating release of hormone.³ We are not aware of studies evaluating the effectiveness of injectable medroxyprogesterone in these instances. In our case the patient was not obese and did not remember rubbing her injection site. Likewise, no studies have shown that one failure with injectable medroxyprogesterone increases the likelihood of repeated failure, or that

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failure with injectable medroxyprogesterone means that failure with other progesterone-only birth control methods (mini-pill, levonorgestrel implants) is more likely.

The possible teratogenicity of in utero exposure to steroid hormone preparations has been an issue of great concern for the last three decades.⁴⁻¹⁵ Many of the early studies on this issue did not distinguish among hormone preparations, but grouped all exposures together to achieve significant numbers. Also, much of the concern about teratogenicity centered around hormonal pregnancy tests and hormonal supplementation for threatened abortion, neither of which is commonly prescribed today.

Reports on the possible adverse fetal effects of injectable medroxyprogesterone and oral medroxyprogesterone (Provera) first surfaced in 1964 with a case of transient neonatal clitoral hypertrophy following in utero exposure to oral medroxyprogesterone.⁴ A second study reported simulated congenital adrenal hyperplasia after a similar in utero exposure.⁵ In this case, as in the first one, the abnormality reverted to normal by the time the child was 1 month old.

Later reports examined the possible correlation between exposure to the progesterone in pregnancy tests (dosage range unspecified) and any one of a series of malformations characterized by the VACTERL acronym (vertebral, anal, cardiac, tracheal, esophageal, renal, limb). The reports concluded that exposure leads to a relative risk of 2.75 for at least three of the major malformations associated with VACTERL as well as a relative risk (RR) of 6 for congenital cardiac defects alone.^{6,7}

A study of 11,468 babies born in West Jerusalem also examined in utero exposure to a heterogeneous group of steroid hormones and reported that the group of 432 babies born after exposure had a 26 percent higher incidence of major malformations and a 33 percent higher incidence of minor malformations than unexposed babies. The major malformations most commonly reported were congenital heart disease, cleft palate, and positional foot deformities.⁸ Another study of more than 50,000 pregnancies echoed these results and reported a relative risk of 1.5 for congenital heart disease after fetal exposure to oral medroxyprogesterone.⁹ As for who might be at higher risk, one report, a study of 715 malformed infants, concluded that the use of oral

contraceptives around the time of pregnancy caused a greater risk of fetal malformation in older compared with younger mothers and that male infants tended to be affected more often than female infants.¹¹

A large retrospective study in Thailand that was the subject of several reports revealed the most specific data about in utero exposure to injectable medroxyprogesterone.¹³⁻¹⁵ The 1431 children exposed to injectable medroxyprogesterone had higher neonatal (RR = 2.2) and infant (RR = 2.2) mortality rates, but most of the increased mortality was attributed to low birth weight.¹⁴ The authors recognized that some of the differences were due to confounding variables. For example, none of the pregnancies exposed to injectable medroxyprogesterone were planned, but all of the comparison pregnancies were planned. The risk factors associated with an unplanned pregnancy and the lower participation in prenatal care among the exposed groups could not be separated from the effect of the exposure itself.¹³ The study also noted an increased risk of polysyndactyly (RR = 4.8) and chromosomal anomalies (RR = 5.5) in the group exposed to injectable medroxyprogesterone; however, in one half of these cases the last injection of medroxyprogesterone occurred more than 3 months before conception.¹⁵ No increased incidence of cardiovascular anomalies, hemangiomas, or other VACTERL anomalies was noted.¹⁵

In contrast to results from those reports, multiple studies have found little association between in utero sex hormone exposure and fetal abnormalities.^{9,12,16-34} Included in these reports are two World Health Organization Bulletins, which state that in utero exposure is not likely to be a public health problem because pregnancy with injectable contraceptives is uncommon, disorders are infrequent, and any potential teratogenic risk is small.^{16,17} Another review article concluded that no contraceptive method substantially increased fetal risks over the 2 to 3 percent likelihood any given pregnancy has of resulting in anomalous offspring.¹⁸ Others agreed, stating that if there are increased risks of nongenital malformations associated with sex steroids, the risks are very small, might not be causal, and are substantially below the spontaneous risk for malformations.¹⁹

Only four articles address the possible long-

term side effects of in utero exposure to injectable medroxyprogesterone. The earliest stated that in utero exposure to progestogens did cause personality differences, and exposed children were more independent, sensitive, self-assured, and self-sufficient than both unexposed siblings and children exposed to estrogen in utero.³⁵ A later study showed progestogen exposure had no effect on cognition, but did have a questionable demasculinizing effect and a questionable effect on the development of sexually dimorphic behavior. Exposure did not appear to have any bearing on sexual orientation.³⁶ As for intellectual development, children exposed to injectable medroxyprogesterone in utero showed no difference from controls.³⁷ In addition, the physical growth and development of children exposed to injectable medroxyprogesterone in utero were normal with the exception of a slight delay in the development of pubic hair in girls.³⁸

Conclusion

Depo-Provera is a form of contraception that has the advantage of requiring only one injection every 3 months and has quickly become a popular form of birth control in the primary care setting. Although it is very effective, failure does occur and can cause exposure of the developing fetus to the hormone. Sex hormone exposure has been linked to a number of possible congenital anomalies, from clitoral hypertrophy to simulated congenital adrenal hyperplasia to any of the VACTERL group of malformations, but most of the literature reviewed suggests that the absolute risk of an anomaly due to an exposure is either no different from or only minimally higher than the overall spontaneous malformation rate. There is concern, however, that exposure could lead to low birth weight and the possible morbidity and mortality associated with it.

No studies have yet proven any significant long-term side effects associated with in utero exposure to injectable medroxyprogesterone. Overall, injectable medroxyprogesterone should remain a category X medication, as there appears to be little benefit to administration of the drug during pregnancy. Patients and physicians alike should be reassured, however, by the low teratogenicity of the drug when, as in the case presented here, accidental exposure occurs during pregnancy.

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