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SAFETY OF MEDROXYPROGESTERONE IN PREGNANCY

Question:
What are the risks associated with inadvertent exposure to depot-medroxyprogesterone in the first trimester of pregnancy?

Answer:
There have been 14 cases of ambiguous genitalia reported to the FDA following use of progestogenic hormones in pregnancy[1]. This appears to be more associated with the 19-nortestosterone derivatives (e.g norethynodrel, norethindrone) rather than medroxyprogesterone. Based on these reports, the FDA stipulated that pregnancy-related indications (e.g. prevention of spontaneous abortion) for progestogens should be withdrawn[1].

In the Michigan Medicaid surveillance study, 407 newborns had been exposed to medroxyprogesterone during the first trimester. Fifteen major birth defects were observed (13 were expected in the general population) which included (observed/expected) cardiovascular defects (7/4), and oral clefts (1/1). This suggests an association between the use of medroxyprogesterone and cardiovascular abnormalities, although other factors including chance cannot be discounted[1].

The Collaborative Perinatal project assessed 866 pregnancies with first-trimester exposure to progestogens including 130 to medroxyprogesterone. Increased occurrence of cardiovascular defects (e.g. ventricular septal defect) and hypospadias was observed with progestogens as a class. Closer assessment e.g. with regard to timing of exposure, failed to support an association between progestogens and non-genital malformations[1].

A study of 2754 infants who were born to mothers with first-trimester vaginal bleeding identified 1608 newborns whose mothers took medroxyprogesterone, 17-hydroxyprogesterone or both in the first trimester with almost 80% (1274) taking oral medroxyprogesterone 20-30mg/day alone. No significant difference was observed in the rate of malformations compared with a control group which was 1146 infants whose mothers had untreated vaginal bleeding in the first trimester[1].

In a cohort study where 988 progestogen-exposed pregnancies (60 to medroxyprogesterone) were compared with 1976 unexposed controls, no difference in foetal malformations was observed[1].

Medroxyprogesterone has been trialed to prevent spontaneous abortion or threatened abortion in doses of 80-120mg/day starting from the 5th to 7th week of pregnancy, until at least the 18th week of pregnancy. No statistically significant difference was observed in the incidence of congenital anomalies occurred in the medroxyprogesterone group (4.1%; n=449) compared with non-exposed controls (3.5%; n=464)[2].

Conclusions:
There is a reasonable amount of information describing the use of progestogens in the first trimester of pregnancy. The majority of the data is reassuring and suggests that medroxyprogesterone is not overtly teratogenic. However, it is impossible to completely guarantee drug safety during this period and the possibility of cardiovascular and genital abnormalities cannot be excluded.

References:
1. Briggs GG *et al.* Drugs in pregnancy and lactation (5th ed), 1999
2. Drugdex, Micromedex database

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