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CASE REPORTS

Normal pregnancy outcome after inadvertent exposure to long-acting gonadotrophin-releasing hormone agonist in early pregnancy

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Five infertile women exposed to long-acting gonadotrophin-releasing hormone agonist (GnRHa) during early pregnancy were studied to assess the risks of embryotoxicity on the outcome of their pregnancies. All the patients were diagnosed as stage 3–4 endometriosis following laparoscopy. Long-acting GnRHa (3.75 mg) was given in the first 3 days of their preceding menstrual period. Four of the five patients had two GnRHa injections and the last patient had three GnRHa injections. All patients were advised to use a barrier contraception (condoms) throughout the treatment period. Since all complained of no bleeding following the initial injections, human chorionic gonadotrophin (β-HCG) concentrations were tested in order to rule out any pregnancy. Ultrasonographic examinations were commenced routinely and all patients had amniocentesis at 16–18 weeks gestational age. Genetic analysis revealed a normal karyotype in all fetuses. All five pregnancies progressed to term without complication, and normal healthy infants were delivered. Although there are still no clear answers concerning teratogenic and hormonal effects of GnRHa exposure in pregnancy, our data may suggest that luteal function, genetic structure and pregnancy outcome are not adversely affected by GnRHa. Since possible subtle effects on fetal endocrine organs cannot be disregarded, close monitoring is still needed in GnRHa-exposed pregnancies.

Key words: GnRHa/luteolysis/pregnancy/teratogenicity

Introduction

Increasingly, gonadotrophin releasing hormone agonists (GnRHa) are being used in gynaecology and infertility for their hypogonadotrophic effect in the treatment of leiomyomata and endometriosis. Pituitary desensitization with GnRHa prior to exogenous gonadotrophin treatment is an adjunct to ovulation induction regimens, reducing cancellation rates of in-vitro fertilization (IVF) treatment and increasing their yield of eggs, embryos and successful pregnancy rates (Hughes *et al.*, 1992). With increased use, clinicians are frequently challenged by early pregnancies with unrecognized exposure to GnRHa. However, there is little information regarding incidence, teratogenic effects, the outcome of such pregnancies, and how they should be managed.

Since there is no consensus on the appropriate management of GnRHa-exposed pregnancies and these patients have been suffering from infertility for a long period, we report the outcome of five GnRHa-exposed pregnancies.

Case presentations and results

Five women ranging in age from 24 to 36 years who underwent diagnostic laparoscopy for primary infertility were included in the study. The duration of infertility was 3–16 years, and all male partners had adequate semen analysis. All women were diagnosed with stage 3–4 endometriosis and were given long-acting GnRHa (depot Decapeptyl®, 3.75 mg) for 6 months commencing in the first 3 days of their initial menstrual period. The couples were strictly advised to use condoms as contraception during treatment, to prevent possible pregnancy. All five women complained of secondary amenorrhoea after treatment commenced, so they were tested for β-human chorionic gonadotrophin (β-HCG) concentrations to establish pregnancy dates; all five were found to be pregnant. None of them had used condoms as contraception. Clinical data for all five patients are shown in Table I. Four of the five patients had two injections of GnRHa and the last patient had three injections at the time of diagnosis. Gestational age determined by vaginal sonography was between 6 and 8 weeks at diagnosis. Each couple was counselled regarding the possible teratogenic effects of GnRHa exposure and all decided to continue with the pregnancy. Upon diagnosis, serum β-HCG and progesterone concentrations were measured serially. The increase in serum β-HCG concentrations was normal (>70% increase every 2 days) and all had serum progesterone concentrations >25 ng/ml. Ultrasonographic examinations were commenced routinely and revealed normal findings. All patients opted for genetic amniocentesis at 16–18 weeks of gestational age and the fetuses were found to have normal karyotype. Since they were diagnosed late, none of the women received any luteal support. No structural defects were observed at 20 weeks of gestation by ultrasonography. All five pregnancies proceeded uneventfully to 40 weeks gestation and normal healthy infants were delivered with a mean birth weight of 3240 ± 370 g. Table II shows data for pregnancies exposed to GnRHa reported in the literature.

Table I. History of the patients

Case no.	Age (years)	Pregnancy diagnosed with USG at (weeks)	No. of injections/ dose mg	Birth weight (g)	Karyotype	Duration of infertility (years)	Gestational age (weeks)
1	24	6	2/7.5	3440	46 XX	4	40
2	29	7	2/7.5	3100	46 XX	5	38
3	25	6	2/7.5	3570	46 XX	3	39
4	36	6	2/7.5	2950	46 XY	16	38
5[a]	27	8	3/11.25	3400	46 XX	5	40

[a]This patient was diagnosed to be pregnant soon after the third injection of depot triptorelin acetate.
USG = ultrasonographic evaluation.

Table II. Reported pregnancies in literature exposed to GnRH agonist

Author	Agonist	No. of pregnancies	No. of babies	No. of abortions	No. of ectopic pregnancies
Martinez *et al.* (1988)	Bus	3	4	0	0
Ferrier *et al.* (1988)	Leu	1	1	0	0
Serafini *et al.* (1988)	Leu	2	0	1	1
Chetkowski *et al.* (1989)	Leu	1	0	0	1
Dicker *et al.* (1989)	Bus	1	1	0	0
Forman *et al.* (1990)	Bus	3	1	0	2
Golan *et al.* (1990)	Trp	1	1	0	0
Isherwood *et al.* (1990)	Bus	8	3	5	0
Lejeune *et al.* (1990)	Bus	2	2	0	0
Smitz *et al.* (1991)	Bus	13	7	3	3
Ghazi *et al.* (1991)	Leu	1	1	0	0
Herman *et al.* (1992)	Dec	11	7	4	0
Lockwood *et al.* (1992)	Bus	5	4	1	0
Jackson *et al.* (1992)	Bus	6	5	1	0
Har-Toov *et al.* (1993)	Trp	1	1	0	0
Balasch *et al.* (1993)	Bus/Leu	14	13	1	0
Weissmann & Shoham (1993)	Trp	1	1	0	0
Cahill *et al.* (1994)	Bus	25	22	3	0
Elefant *et al.* (1995)[a]	Trp	28	24	4	0
Taskin *et al.* (1999)[a,b]	Trp	5	5	0	0

[a]Depot GnRHa.
[b]This report.
Bus = buserelin acetate; Leu = leuprolide acetate; Trp = triptoreline acetate.

Discussion

The reported number of patients who were exposed to GnRHa in early pregnancy is increasing due to the wide use of GnRHa in gynaecological disorders. The popularity of in-vitro fertilization (IVF) and inevitable use of GnRHa to produce pituitary desensitization prior to ovarian stimulation have further increased exposures of early pregnancies to this drug. In a meta-analysis reviewing the efficacy of various GnRHa regimens, the authors concluded that the addition of GnRHa down-regulation to ovulation induction regimens for assisted reproductive technology was advantageous (Hughes *et al.*, 1992). Although the number of reported deliveries following exposure is increasing, data regarding embryotoxicity and how the exposed pregnancies should be managed are still lacking. Despite the strict advice on the use of contraception, many women are prepared to accept the risks of exposure rather than using contraception during treatment with GnRHa due to their long period of infertility.

Since this early drug exposure is not yet preventable, we should address the problems and gather the relevant data regarding effects of agonists on early pregnancy. Most of the data reported to date are related to the use of short-acting GnRHa in IVF procedures. Thus it appears that the pregnancies occurred either just before or at the beginning of GnRHa administration. Therefore the exposure has encompassed only the early stage of embryonic development and not organogenesis. The consequences of this early exposure are mainly luteolytic effects and/or embryotoxicity. Although the delayed effects on children cannot be evaluated, preclinical toxicology studies revealed no malformations in different species (Elefant *et al.*, 1995). The potential for adverse effects from GnRHa exposure in early pregnancy is probably related to the manipulation of the fetal hypothalamic–pituitary–placental axis. Some physiological effects of GnRHa on pregnancy and the fetus have been studied. While GnRHa has been shown to have luteolytic properties, its use in attempts to interrupt pregnancy has been unsuccessful (Skarin *et al.*, 1981). It appears that HCG from the trophoblast easily overrides the luteolytic effect (Lanzone *et al.*, 1989). Eley studied the effect of GnRHa in pregnant baboons (Eley, 1987); while there was a transient decline in progestins, the study could not determine whether abortions were related to it. Cahill *et al.* have reported pregnancy loss in GnRHa-exposed women not greater than that reported previously in infertile women following natural

or IVF conceptions and suggested that there is no need for supplementary treatment (Cahill *et al.*, 1994). Sopolek and Hodgen found that GnRHa infusion did not affect the maternal hormone concentrations and that in-utero exposure to GnRHa after day 35 had little effect on overt gonadal development (Sopolek and Hodgen, 1987).

Our data are different from the above, since we included patients exposed to long-acting GnRHa. Besides, the length of exposure in our study is longer than the reported cases which appears to be at least 6–8 weeks of pregnancy possibly extending to the stage of organogenesis. It would be reasonable to assume that luteal function is more likely to be impaired in cases with long-acting GnRHa, since it cannot be interrupted when pregnancy is diagnosed, thus allowing extended fetal exposure to the drug. In our cases, there were no abortions or fetal deaths. The increase in serum β-HCG concentrations was normal and the progesterone concentrations were consistently >25 ng/ml. Since the pregnancies were diagnosed relatively late, no luteal supplementation was given to the patients. Similarly, Elefant *et al.* have reported no adverse changes in pregnancy exposed to depot GnRHa (Table II) (Elefant *et al.*, 1995). The above and our data support previous reports that luteal function is relatively resistant to exogenous GnRHa (Smitz *et al.*, 1991; Cahill *et al.*, 1994). These results are further supported in a recent study reporting that continuous GnRHa administration in the luteal phase does not impair corpus luteum function, suggesting that HCG is the main force for the development of the corpus luteum (Valbuena and Simon, 1997).

Embryotoxicity is potentially the most important issue, which is more difficult to outline since most of the exposed cases encompassed the early stages of embryonic development. Of 79 babies born, there have been only two cases with congenital abnormalities: one with cleft palate (Herman *et al.*, 1992), the other with bilateral talipes equinovarus (Jackson *et al.*, 1992). To date, there have been no reported series with genetic amniocentesis despite normal pregnancy outcomes. Although we had a small series of patients, all agreed to amniocentesis, which revealed normal karyotypes. In contrast to our findings, in only one earlier case did amniocentesis reveal a trisomy 18 karyotype (Young *et al.*, 1993). It is clearly evident that in our patients the drug exposure has extended to the stage of organogenesis but resulted in normal pregnancy outcome. Obviously the assessment of fetal risk requires large numbers of cases. However, our results along with others (Abu-Heija *et al.*, 1995) are reassuring despite some observed abnormalities in rats producing the earlier fears about teratogenicity. Moreover, the genetic testing and the normal pregnancy outcome, despite longer drug exposure, in our patients along with the other reported cases may further question the possible embryotoxicity of GnRHa in humans.

Having no strong evidence of teratogenetic effects of GnRHa in humans, it would be logical not to terminate these pregnancies based on the drug exposure alone despite potential fetal morbidity. Also we may consider β-HCG concentration measurements in GnRHa-injected women before each injection. Couples should be counselled regarding the possible effects and should be aware of the possible outcome of GnRHa-exposed pregnancies reported. Although possible subtle effects on fetal endocrine organs cannot be disregarded, physicians should proceed with caution and closely follow-up the patients. In addition, delayed evaluation of the exposed children later in their lives should be carried out to observe any effects on their future reproductive function. We agree with others that there should be a central registration for the outcomes of GnRHa-exposed pregnancies to enable the detection of any related defects.

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