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Case Report

Early Pregnancy during Long-acting GnRh Agonist Luteal Exposure for IVF Cycle

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Abstract

Luteal administration of gonadotrophin releasing hormone agonists (GnRHa) in a long protocol is a usual protocol to induce pituitary down-regulation before Controlled Ovarian Stimulation (COS) in IVF. GnRHa is recommended to be started in the luteal phase of the previous cycle of the COS, in order to avoid flare-up effect and cyst formation, potentially induced by the initial LH/FSH surge. Some reports of inadvertent long-acting GnRHa-exposed pregnancies raise questions about the possible teratogenic effects and the potential effects of GnRHa on corpus luteum, implantation and gestation. We performed a retrospective study in our Reproductive Medicine Unit of 449 IVF cycles of GnRHa long protocol. Five patients underwent uneventful pregnancies and gave birth at term to five healthy babies. Incidence of inadvertent long-acting GnRHa-exposed pregnancy was 1.1%. The five couples shared some characteristics: all women had been referred for secondary infertility and had partial tubal damage. Sperm parameters were normal or subnormal. With 12 months of follow-up, the childrens development was considered as normal. After more than 30 years of clinical experience, no teratogenic effect of GnRHa has been observed. However, despite a reassuring literature, no long-term follow-up has ever been published. Long-acting GnRHa has a duration of action of 28 days and its release must be completely achieved before the beginning of the organogenesis (at 6 gestational weeks). Regarding the potential luteolytic effect of GnRHa, delivering GnRHa seven days after conception wouldn't have any impact on corpus luteum function. The debate relates currently more to the role of GnRHa on the embryo implantation. Our report suggests that clinicians should be attentive with medical profile (secondary infertility, tubar permeability, subnormal sperm) when women are exposed to long-acting GnRHa in their luteal phase, and maybe should advise mechanical contraception for these couples during the month of the down-regulation.

Keywords: GnRH agonist, GnRHa long protocol, IVF, Pituitary desensitization, Pregnancy, Teratogenicity

Introduction

IVF needs to induce a controlled ovarian stimulation (COS) in order to retrieve a sufficient number of oocytes and to obtain sufficient embryos to optimize the chance of pregnancy. For Sunkara et al., about 15 oocytes retrieved give the best chance of live birth rates [1]. Luteal administration of gonadotrophin releasing hormone agonists (GnRHa) in a long agonist protocol is a usual protocol to induce pituitary down-regulation before Controlled Ovarian Stimulation (COS) for IVF [2]. The two reasons for using GnRHa before COS are to synchronize follicular recruitment and to prevent an endogenous uncontrolled LH surge during the ovarian stimulation [3]. Long-acting GnRHa may be prescribed in the follicular or in the luteal phase of the cycle. When possible, authors recommend to start using GnRHa in the luteal phase of the previous cycle, in order to avoid cyst formation, potentially induced by the initial LH/FSH surge (flare-up effect) [4]. Although some Reproductive Medicine Units advised mechanical contraception during the initial period of down-regulation, patients may present some hesitations to use contraception while they are actively trying to have a child [5]. In this way, some reports have described cases of GnRHa- exposed pregnancies [5-9]. In most of the case reports, no teratogenous effect have been described. However, only the small and very controversial study of Lahat et al. reported a long term follow-up at 7.8 ± 2 years and suggested from six cases an increase of physical or neurodevelopmental abnormalities [10,11]. Furthermore, there are many differences between the reports, with regards to the GnRHa used (long-acting or short-acting GnRHa, various molecules used ...), the protocols used and the data collected. In many reports, the authors discussed the potential luteolytic role of the GnRHa, but since about ten years, some

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studies about the role of GnRHa administration at the time of implantation on the embryo developmental potential may restart both discussions [12-14]: is there a teratogenic effect and is there a luteolytic action of GnRHa? In this study, we present five inadvertent long-acting GnRHa-exposed pregnancies observed in our Reproductive Medicine Unit, and then examine the effects of GnRHa on corpus luteum, implantation, gestation, delivery and birth rate in light of the literature.

Cases Reports

Between January 2012 and December 2012, 449 cycles of long protocols of IVF have been performed in our Reproductive Medicine Unit (University Teaching Hospital de la Conception, Marseille, France). Pituitary desensitization was achieved by administration of long-acting triptorelin (Decapeptyl LP 3 mg, IpsenPharma Biotech, Signes, France) in the luteal phase of the previous cycle before IVF. In our centre, patients were not advised to use barrier contraception. When spontaneous pregnancy had been discovered, the prescription of a luteal support was determined at physician's discretion. We report five cases of early gestation exposed to a midluteal phase GnRHa administration. Patients' characteristics are summarized in Table 1.

Case 1

The first case is a couple of patients with 4 years of secondary infertility due to a polycystic ovary syndrome and a male factor. The man had already two children with his first wife, without referring to IVF. However, 25 years later, his sperm showed a moderate oligoasthenospermia. His new wife was 35 year-old and she had two intra-conjugal early miscarriages. She underwent 2 unsuccessful attempts of homologous intrauterine insemination prior to IVF. For their first attempt of IVF, the patient began the pituitary desensitization with one intra muscular injection of triptorelin depot, starting on day 22 of her menstrual cycle. Fifteen days later, the patient was still in amenorrhea. The pregnancy test was positive, and the ultrasound confirmed an intra-uterine pregnancy of approximately 4 weeks of gestation. No luteal support was administered. The pregnancy continued uneventfully until 28 weeks of amenorrhea. At this term, the patient had to be admitted to the High-Risk Pregnancy Department, because of an imminent preterm delivery. Intra-venous nicardipine had to be infused. At 35 weeks of gestation, the patient had a premature rupture of membranes and a healthy girl weighing 2790 g was delivered vaginally. After a follow –up of 12 months, her development was judged as normal.

Case 2

A 34 year-old woman was referred to our Reproductive Medicine Unit because of 4 years of secondary infertility due to a male factor. She had normal ovulatory cycles and permeable fallopian tubes. Her husband was 44 years-old and his sperm showed a severe oligoasthenoteratospermia. Four years earlier, she had a spontaneous pregnancy after 2 unsuccessful cycles of homologous intra-uterine insemination. After 5 attempts of homologous intra-uterine insemination, she was referred to IVF. During the first IVF cycle, 2 embryos were transferred without pregnancy. The patient began a second cycle of IVF with one injection of triptorelin depot on day 22 of her menstrual cycle. Fifteen days after the GnRHa injection, the patient was still in amenorrhea. The hCG level was of 5106 mUI/l and oestradiol of 336 pg/ml. Progesterone support was given until the twelfth gestational week and the patient had an uneventful pregnancy. At 38 weeks of gestation, a healthy baby girl weighing 2950 g was delivered vaginally. At the age of 4 months, no clinical abnormality was observed.

Case 3

A couple was referred for 18 months of secondary infertility due to a female factor. The husband had normal sperm parameters. The woman had a right ectopic pregnancy two years before, leading to a right salpingectomy. For the first attempt of IVF, triptoreline depot was injected on day 22 of her menstrual cycle. Fifteen days later, she presented with amenorrhea. The serum hCG-level was of 16187 mUI/l. The ultrasonography confirmed an intra-uterine ongoing pregnancy. No luteal support was administered. The patient went into spontaneous labour at 39 weeks' gestation and gave birth to a healthy girl weighing 3310 g. After 3 months of follow-up, the baby was considered as normal.

Case 4

A 33 year-old woman with a history of endometriosis and left tubal occlusion was referred to IVF because of two years of secondary infertility. Twelve years before, she had a spontaneous pregnancy with her first husband and another pregnancy with her current husband three years before. Her husband exhibits moderate teratospermia. For the first attempt of IVF, triptorelin depot was injected on late luteal period. Fifteen days later, the serum hCG level was of 15527 mUI/ml. No luteal support was administered. The pregnancy went normally to term and the patient had spontaneous normal vaginal delivery at 38 gestational weeks. She gave birth to a healthy girl, weighing 3560 g. Twelve months later, the pediatric examination was considered as normal.

Case 5

A couple with a 30 year-old woman and a 26 years-old man, was referred after two years of secondary infertility. The woman

Case n°	Age (m/f)	Duration of infertility (yrs)	type	Aetiology	Lo,g acting GnRHa used	Luteal support	Pregnancy	Term at delivery (WG)	Baby gender
1	46/35	4	secondary	PCOS/ male factor	Trp	no	preterm delivery	35	female
2	44/34	4	secondary	male factor	Trp	yes	Uneventful	38	female
3	42/34	1.5	secondary	tubal	Trp	no	Uneventful	39	female
4	33/33	2	secondary	tubal	Trp	yes	Uneventful	38	female
5	26/30	2	secondary	tubal	Trp	no	Pericardiac effusion (21 SG)	36	female

m/f : male/female,GnRHa : Gonadotrophin Releasing Hormone agonist, WG : Weeks of Gestation, PCOS : Polycystic Ovary Syndrome, Trp : Triptorelin depot

Table 1: Characteristics of couples with early pregnancy during luteal phase with inadvertent administration of long acting GnRHa.

had already a child with her first husband, but her right tube was impermeable. The sperm analysis was normal. The patient started the first attempt with the long protocol, doing the injection of triptorelin depot on late luteal period. Fifteen days later, the serum hCG level was of 3756 mUI/ml, and the ultrasonography showed a single gestational sac measuring 20 mm and an embryo with 8.6 m of crown-rump length. No luteal support was administered. At 21 gestational weeks, a minor pericardial effusion has been discovered on prenatal ultrasonography. With a closer follow-up, the pregnancy progressed to term and resulted in the live-birth of a girl delivered vaginaly at 36 gestational weeks, and weighing 2560 g. No cardiac abnormality was observed in the initial newborn clinical examination. A cardiac ultrasonography made on day 3 of life was found to be normal. At 12 months-old, her physical and psychological development was considered as normal.

Discussion

Since its discovery and synthesis in 1971 [3], the use of GnRHa is increasing in gynaecologic disorders especially in vitro fertilization and endometriosis. Consequently, some cases of inadvertent GnRHa-exposed pregnancies have been reported. However, and surprisingly compared to the number of IVF cycles in the world, only 30 cases of long-acting (LA) GnRHa-exposed pregnancies have been described. Our rate of inadvertent LA-GnRHa-exposed pregnancy is of 5/449 (1.1%), which is a similar incidence compared to what is described in the literature since 20 years (Platteau, Gabbe et al. 2000). As previous authors, we didn't observe any miscarriages or congenital abnormalities. Interestingly, we observed that the five couples shared some characteristics: all patients had been referred to IVF because of secondary infertility (and not primary), all the women had partial tubal damage, and the sperm parameters were normal or subnormal in all cases. This is not surprising, because one knows that a previous history of pregnancy is a good prognostic factor in IVF [15,16]. Partial tubal damages are also conditions that may allow normal fecundation and implantation. Finally, it is well described that semen has a large intra-individual variability and that there is an extensive overlap between the fertile and the infertile men with regard to their semen parameters [17]. Our report suggests that clinicians should be attentive with such patients' profile when there are exposed to long-acting GnRHa in midluteal phase.

Nevertheless, our results are limited for at least three reasons: firstly, we have a small number of patients, secondly, there may be early miscarriages in the long protocol that were not diagnosed, interpreted as menses, and finally, further follow-up would help us to conclude that long-acting GnRHa is a safe drug for the future development of the newborn child. However, regarding the potential teratogenicity of the GnRHa and in spite of the placental transfer of GnRHa, most of the studies published in the last two decades seem to be reassuring. In these reports, the rate of developmental abnormalities such as clef palate or hypospadias was not different from what is observed in spontaneous pregnancies [11].

Only few studies have more than a one year follow-up. In 1994, Cahill et al. published data from 25 inadvertent buserelin-exposed pregnancies [6]. No specific follow-up of these babies had been foreseen, but three years later, all children had been reported as 'normal' by their parents. In 1998, Chardonnens et al. reported 4 cases of early gestation occurring during inadvertent triptorelin administration [7]. In one of these cases, the woman gave birth to a healthy boy. Six years later, his development both mentally and physically was considered as normal. Another patient gave birth to twins, and they were also considered as normal at 14 months-old. Additionally, these latter studies reported exposition to short-acting GnRHa. The only one pregnancy exposed to long-acting GnRHa in Chardonnens' report ended in an early miscarriage at 6 weeks of gestation [7]. To our knowledge, only one report has carefully examined the developmental of children born after inadvertent administration of long-acting GnRHa in early pregnancy, using codified psychological tests. In this study, Lahat et al. found neurodevelopmental abnormalities in four of six children, including attention deficit hyperactivity disorder, motor deficits and speech deficits [10]. However, this report was based on a low number of patients (n=6), and there is no data concerning the maternal behaviour during pregnancy. Moreover, the molecules of long-acting GnRHa used are not specified in this study. Papanikolaou et al. described the achievement of pregnancy three times in the same patient during luteal short-acting GnRHa administration [9]. One pregnancy ended in spontaneous abortion and the other two resulted in the delivery of two girls. At the time of the report, the girls were 3 ½ and 7 years-old, and the older one had been diagnosed with attention deficit hyperactivity disorder, and dyslexia. From our point of view, these pathologies are common and multifactorial, and there are yet no valuable and molecular data that could link the exposition of GnRHa during early pregnancy and such neurodevelopmental abnormalities. However, these observations show that clinicians must be attentive with GnRHa-exposed children.

Additionally, the question of the type of GnRHa used is an important issue, because in case of short-acting GnRHa-exposed pregnancy, the potential deleterious effect of GnRHa consists essentially on the corpus luteum function. For long-acting GnRHa, the question is also their possible teratogenicity, and mainly their long-term effect on the exposed children. Indeed, despite 20 years of case reports, no author has described the evolution of these medical histories; particularly there is no information about the puberty and/or fertility of the exposed children. Many authors have considered that since the long-acting GnRHa have a duration of action of 28 days, their release is completely achieved before the beginning of the organogenesis (at 6 gestational weeks). However, firstly, complete removal of the product is obtained in 42 days, which additionally may be different from one patient to the other. Secondly, the ontogenesis of the pituitary seems to be an early event during embryogenesis, possibly when patients are still exposed to long-acting GnRHa [18]. Furthermore, studies in animal models showed skeletal anomalies and increased rates of fetal death in the offsprings of buserelin-exposed pregnant rabbits [19] and a reduction of testicular weight in male Rhesus monkeys [20].

Thus, we suggest, as others, that, because the long-term outcomes of inadvertent exposure to long-acting GnRHa are still unknown, there should be a register for GnRHa-exposed pregnancy, with a closer long term follow-up, especially for patient and children exposed to long-acting GnRHa. The other possibility is to use only daily GnRHa, but this doesn't enable the practitioner to completely reassure women, since GnRHa are still classified as category X product by the Food and Drug Administration.

In 1979, Casper et al. published their conclusions about the luteolytic effect of the GnRH agonists (at that time called Luteinizing Hormone-Releasing Factor) [21]. They found that the injection of 50 μg of a long-acting analog of GnRH in midluteal phase induced a premature menses, which was logically associated with luteolysis (as shown by the decline of progesterone levels). Indeed, it is well-known that normal luteal LH levels are needed for proper corpus luteum function [8]. In this way, Asch et al. showed that in the rhesus monkey, GnRHa induced luteolysis when given on days 3 and 5 post ovulation [22]. However, attempts to interrupt early pregnancy by using the potential luteolytic effect of GnRHa has always failed in humans. Indeed, Asch et al. also showed that no effect was observed on corpus luteum when GnRHa were given on day 7 post ovulation [22]. This may be due to the main role that plays hCG in rescuing the corpus luteum function. Reporting the cases of 11 pregnant patients inadvertently exposed to a long-acting GnRHa during periovulatory, midluteal or late luteal period, Herman et al. showed that impaired corpus luteum function possibly depends on the day of GnRHa injection [8]: the potential luteolytic effect may be avoided by the secretion of hCG in the late luteal period. This latter assumption is supported by Valbuena et al., who showed in their prospective and randomized study of 38 ovum donors that the corpus luteum is primarily driven by the hCG [23]. Taskin et al. also found that the increase in serum hCG concentrations was normal in five patients exposed to long-acting GnRHa in mid-luteal phase and that all patients had serum progesterone concentrations > 25 g/ml [24]. In our five cases, we didn't observe any abnormality in the progress of the serum hCG level. The fact that through more than 30 cases reporting exposition to long-acting GnRHa during early pregnancy, no author found an increased rate of early miscarriage is also in agreement with this hypothesis.

Moreover, some authors have suggested that GnRHa could play a positive role in fertility [13]. Tesarik et al. compared the implantation rate between two groups of IVF patients, one group receiving an injection of triptorelin 0.1 mg 3 days after embryo transfer, the other one receiving the solvent only (placebo) [12]. They showed that implantation and pregnancy rate tended to be significantly higher in the GnRHa group. They assumed that this may be due to a direct effect of the GnRHa on the early-implanting embryo, via a stimulation of the hCG production. This data is in accordance with in vitro and in vivo studies showing that GnRH and GnRHa stimulated placental hCG production [25,26], and thus may maintain a correct corpus luteum function.

As to luteal supplementation, in the cases of inadvertent pregnancy during pituitary desensitization, most of the reports concluded that there is no need to use it. This is in agreement with the theory that the corpus luteum is able to produce progesterone, via the hCG stimulation. In our cases, luteal supplementation depended on the decision of the physician, and we didn't observe any difference between supplemented pregnancies and non-supplemented pregnancies.

Conclusion

In conclusion, after more of 30 years of clinical experience for the use of long-acting GnRHa, no teratogenic effect has been observed. However, despite reassuring literature, since no long-term follow-up has ever been published, we recommend a watchful approach, particularly with respect to the gonadotropic axis of the children. Regarding the potential luteolytic effect of GnRHa, several contradicting reports have been published, but the recent literature seems to prove that delivering GnRHa seven days after conception doesn't have any impact on corpus luteum function. The actual debate is rather the role of GnRHa on the embryo implantation than its potential impact on corpus luteum function.

More recently, GnRH agonist was introduced for luteal phase support. Evidence from in vitro studies suggests that GnRH agonist acts directly on the preimplantation embryos as its receptor is extensively expressed in human morula and blastocyst embryos 6. Porcine and murine preimplantation embryo development is enhanced when embryos are incubated with GnRH agonists and diminished when incubated with antagonist [7,8].

Because of the potential embryonic/fetal effects, adverse perinatal outcomes and congenital malformations are important safety outcomes, and they have been scarcely reported. There is a lack of information regarding the fetal safety of GnRH agonist use in early pregnancy and an apparent inconsistency among the clinical studies' results.

There is evidence that adding GnRH agonist during luteal phase improves ongoing pregnancy. However, this evidence is of very low quality and there is no evidence about adverse perinatal outcomes and congenital malformations. We therefore believe that including this intervention on clinical practice would be still premature.

Conflict of interest

Authors declare no conflict of interest

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