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Embryonic diapause after IVF

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Abstract

Background: A case is presented in which diapause, or implantation which is asynchronous with expected gestational age, is witnessed to have occurred. Since this situation is rarely seen in human reproduction, its implications were examined.

Case: A twin IVF pregnancy, of which one was determined to be Trisomy 21, was reduced to a singleton pregnancy. A discrepancy of the twin implantations was identified with imaging. Cesarean delivery for fetal intolerance to labor occurred after an unremarkable pregnancy. Long- term follow-up of the child provided further insights of the presumed diapause pregnancy.

Conclusion: With there being long-term follow-up of the patient with the physician provider, the perinatal outcome of the presumed placental diapause, appeared to be minimally affected.

Keywords

In-vitro fertilization (IVF); diapause; delayed implantation; Embryo transfer; ultrasound.

Introduction

Infertility is common among the general population, encompassing approximately 10% of all couples. According to data from the National Survey of Family Growth (NSFG) in 2002 an estimated 7.3 million American women age 15-44 years had impaired fecundity. Two million of those women failed to conceive after 12 months of trying [1].

ART is a process that is used to create embryos for uterine transfer, at either the 8-cell stage or as a blastocyst, and some are transferred in the stimulation cycle, while others are transferred after freezing in a more natural cycle. When a competent blastocyst stage embryo finds itself in an unreceptive uterus,

development is delayed. In approximately 100 different species, this delay is reversible; and this embryonic diapause is not considered a general characteristic of all mammals. Once the embryo reaches the blastocyst stage, its metabolism slows down naturally, and in the absence of stimulation from the uterus, there will be no further development. Uterine receptivity may be blocked in response to unfavorable conditions for pregnancy. These interfering conditions may include metabolic, climatic and psychological factors [2-5].

The object of this report is to describe a case of human diapause and to provide a review of the relevant literature.

Case Report

A 43-year-old white female and her Caucasian husband presented for In-Vitro Fertilization (IVF) embryo transfer. The patient was deemed a very reliable historian. There is no history of consanguinity or ingestion of any known teratogen. On day 3, post-oocyte retrieval, 2 three-day 8 cells embryos were transferred. Thirty-two days later, an ultrasound was performed, and a single embryo was seen that measured to be 6 weeks and 3 days. This was compatible with the time of transfer in the cycle. The following week, a second embryo was seen that similarly measured 6 weeks and 3 days, and the other embryo had grown to the equivalent of 7 weeks and 3 days (See Figure 1). From that point on, weekly ultrasounds were performed, until 11 weeks of gestation. Both fetuses followed their expected growth curve and maintained the one-week discordance. The morphology of the embryos was consistent with their assigned gestational age. The couple denied having any intercourse during the IVF cycle and not until the 2 embryos were clearly elucidated. At 11 weeks of gestation, a chorionic villi sampling was performed. The normally grown embryo had trisomy 21 while the smaller embryo was 46 XX karyotype. The trisomic embryo was reduced with an injection of KCl. The remaining fetus continued to grow along its expected growth curve. At 41 weeks of gestation the patient went into spontaneous labor and had a cesarean for fetal intolerance to labor, which was expressed, in the form of persistent severe variable decelerations. The placenta was examined and a Velamentous (VC) cord insertion was found that was otherwise normal. The newborn weighed 2522 gms. at delivery, and the newborn was considered as normal and consistent with the assigned gestation age. Four months later the child was discovered to have a heart malformation double outlet right ventricle. She then underwent an intraventricular tunnel repair. The child is now 7 years of age and her growth and height have consistently remained in the 5th to 7th percentile. Gross motor evaluation was a little behind, but which has now normalized. Her academic performance in school can be described with straight A's, and she seems to be well adjusted.

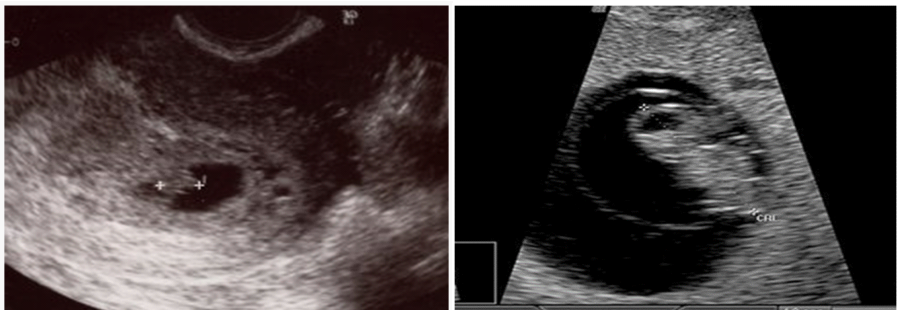

Figure 1: The above image shows the late appearing embryo while the lower image is consistent with the IVF expected gestational age. These images were acquired at the same day.

Discussion

The first description of diapause occurred in 1651 when William Harvey recorded his observations on a Royal hunt. Hunters observed in the Roe deer that the time of mating greatly preceded the time of birth and that the gestational time was too long.

In the 1970's, the ability to culture embryos allowed for the first description of a blastocyst in diapause. Demonstration of this showed the mouse diapause blastocyst arrested cell division in the G1/G0 phase of cell cycling. Both the cell cycle arrest and the decreased metabolism was the hallmark of a diapausal blastocyst. The application of in vitro hormones does not reactivate the blastocyst, but transferring it to a reactivated uterus does induce reactivation of the blastocyst [6]. Human blastocyst expansion may relate to its ploidy [7], which supports the details described in this case.

Seasonal control has been proposed to manipulate diapause in some animals. For this to occur, photoreceptors need to be present in the pineal gland. In natural cycles of humans, there does appear to be seasonal variation in birth. Within the United States and Europe, during the spring there is a minor peak of births followed by a major peak in autumn. This pattern of births has persisted over the last 20 years [8]. However, this seasonal variation is absent in IVF. Kirshenbaum et al in 5,765 IVF cycles over a four-year period of time, were unable to demonstrate any seasonal variation [9].

The suckling, upon neural control of prolactin secretion, may influence lactational diapause [10]. This effect may differ between species. Lactation has been long known to be nature's contraception in humans. Nonetheless, there are numerous women who become pregnant while still lactating, and never have a prior menstrual period. It is possible that some of these women are experiencing lactational diapause. The integrated information is still lacking as to how diapause is induced [11].

In our case report, it appears that implantation of the first embryo occurred 4 days after egg retrieval and that the second embryo implanted 11 days after egg retrieval.

The child in this case was determined to suffer from Double Outlet Right Ventricle (DORV). This entity would not impact implantation since it does occur until Carnegi stage 15-16 which represents days 33 to 37 post fertilization. However, it might affect growth to some degree. This child was born at about the 11^{th} percentile at 2522 gms. Surgical repair of DORV is generally favorable with long-term follow-up.

The placenta had a VC cord insertion, which has been associated with a birth weight of less than the 5^{th} percentile (SGA). Within this case, the child had two reasons to be small at birth, the VC and DORV.

Conclusion

This case report portrays a probable occurrence of diapause in a human. This case was further complicated by the addition of a twin Trisomy 21, a VC placenta and double outlet right ventricle. This report is of value to the literature by virtue of the paucity of diapause reported in humans. Finally, this report shows the value of long-term clinical follow-up, which is uncommonly seen.

Synopsis

Diapause represents implantation which is asynchronous with gestational age, and which is uncommon in humans. A case is reported with its clinical implications.

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