A sporadic case of delayed implantation after in-vitro fertilization in the human?

Jørgen Grinsted1 and Birthe Avery2

Introduction

Delayed implantation, or diapause, is a well described phenomenon in several species of mammals and marsupials, but does not occur in reptiles and birds, because their eggs do not implant (Sandell, 1990; Mead, 1993). Delayed implantation can be induced by lactation, stress, hibernation and the season. In delayed implantation, the embryo becomes temporarily arrested at the blastocyst stage of development. In lactating mice and rats, delayed implantation is obligatory, and in addition, it is easy to induce experimentally by ovariectomy on day 4 of pregnancy. Delayed implantation in mice and rats has thus been thoroughly studied (Nieder and Weitlauf, 1984; Weitlauf, 1985; Oswald and McClure, 1987; Paria et al., 1992, 1993a, 1993b; Tsuji and Nakatsuji, 1992; Weitlauf and Knisley, 1992; Das et al., 1994; and many others). Other examples of species with delayed implantation are marsupials (Bryant and Rose, 1986; Curlewis et al., 1986; Shaw and Renfree, 1986; Fletcher et al., 1988), rabbits, badgers, weasels, minks (Martinet and Allain, 1985; Stoufflet et al., 1989), roe deer (Flint et al., 1994), the Japanese brown bear (Tsubota and Kanagawa, 1993), some bats (Kimura et al., 1987; Van der Merwe and van Aarde, 1989; Funakoshi, 1993; Bernard and Bojarski, 1994), the western spotted skunk (Enders et al., 1986; Berria et al., 1989; Rozell and Mead, 1993), the giant panda (Monfort et al., 1989; Zeng et al., 1992), seals (Temte, 1985; Skinner and Westlin van Aarde, 1989; Reijnders, 1990) and the horse (Vandeplassche, 1986). In the study of excessively prolonged pregnancies in the mare, Vandeplassche (1986) concludes that a diapause of 3-5 weeks is rare, but should be considered to be a reasonable differential diagnosis. In the human, a few cases of delayed implantation have been described after ovarian stimulation and ovulation induction, or in-vitro fertilization (IVF) treatment; however, these pregnancies were only delayed by <2 weeks, as measured by detection of serum human chorionic gonadotrophin (HCG), with most of them ending as spontaneous abortions (Naaktgeboren et al., 1986, 1987; Hamori et al., 1989). In another report, a tubal pregnancy presented itself by a delayed appearance of HCG (Beghin et al., 1992).

When prolonged gestation occurs in the human, one should first try to rule out causes other than delayed implantation, and critically re-evaluate more likely factors, such as a deviant menstrual pattern and reliability of the date for the last menstruation, occurrence of a bleeding not recognized as menstrual, cessation of progesterone pill treatment as a cause of delayed ovulation, and first date for a positive pregnancy test. We present a case here which is highly indicative of a 5 week delay of implantation after IVF treatment. To our knowledge, this is the first report in the literature.

Case report

A 36 year old woman, born in 1958, gravida 7, parity 4, with regular menstruations (3/28) and with a 6 year history of secondary infertility, was admitted to the IVF clinic in 1994 for IVF treatment.

Her previous history was as follows: she had delivered four children, in 1974 (girl, 3000 g/50 cm), 1976 (girl, 3800 g/51 cm), 1979 (girl, 3740 g/52 cm) and 1981 (boy, 3080 g/51 cm) after uneventful pregnancies. The third delivery was apparently delayed by 5 weeks, the fourth by 2 weeks, based on the date of the last menstruation. In 1981 she was sterilized by laparoscopy with bipolar diathermia. In 1988 reversal of the sterilization was performed by laparotomy with tubal...
re-anastomosis. In 1990 the patient was admitted with a positive pregnancy test and 8 weeks of menostasis, caused by a right-sided tubal pregnancy, which was treated with laparoscopic prostaglandin instillation. In 1991 she underwent laparoscopy for loosening of adherences between the omentum and the left salpinx. At that time, both tubes were patent. From 1991 to 1994 she was treated ~20 times with intrauterine inseminations. In 1992 a right-sided salpingectomy was performed, due to another tubal pregnancy. The left tube was observed to be slender, constricted in the middle, with partial phimosis of the ostium, but with fimbriae. In 1994 she experienced a 7 week period of menostasis; however, no signs of pregnancy could be detected, either by ultrasonography or by serum HCG measurement (<10 IU/l).

The patient had thus continuously tried to obtain a viable pregnancy since the tubal re-anastomosis in 1988. Because of that, she was admitted for IVF treatment in October, 1994. On November 15, 11 oocytes were aspirated and fertilized (day 0). Nine of the oocytes cleaved, of which three were transferred to the uterus. The patient was diagnosed non-pregnant, 15 days after oocyte aspiration (November 30), based on a serum HCG <10 IU/l. The coital history in that period was as follows. In November she had intercourse once in the period between the embryo transfer and the negative pregnancy test. After that she did not have intercourse until after she was proven pregnant in January. This was due to the fact that she felt very depressed about not being pregnant, and in addition she became troubled by nausea. During that period she contacted the IVF clinic several times, because of missing menses after the embryo transfer. Ultrasound scans showed that the endometrium was in the secretory phase, indicating that no ovulation had occurred. Another ultrasound scan was performed 7 weeks after oocyte aspiration (January 2), and the HCG was measured. An ultrasound scan now showed endometrium typical of early pregnancy and compatible with early implantation, and the serum HCG was positive at 329 IU/l. The following day (January 3), the serum HCG was 632 IU/l. At 8 weeks after oocyte aspiration (January 11), a 10 mm gestational sac and a yolk sac were demonstrated. Two subsequent ultrasound scans on January 25 and February 24, corresponding to 10 and 14 weeks after oocyte aspiration, showed one live fetus that had grown from a crown-rump length of 8.1 mm to 56 mm during the 4 week period. The calculated age of the fetus 10 and 14 weeks after oocyte aspiration would then be 12 and 16 pregnancy weeks; however, the age of the fetus calculated from the crown-rump length was 6 ± 1 weeks and 12 ± 1 weeks respectively (Figures 1 and 2). The pregnancy continued normally, but was delayed by 4–6 weeks in relation to the IVF treatment, with the expected date for the delivery being between September 4 and 16, instead of August 8, 1995. On September 7, 1995 a normal boy was delivered (4450 g/58 cm). The birth occurred 42 weeks and 3 days after the embryo transfer, corresponding to 44 weeks of pregnancy, or 38–40 weeks of pregnancy corrected for crown-rump length.

Discussion

In the human it is virtually impossible to prove that a discrepancy between the expected and actual length of gestation is caused by delayed implantation. In animal breeding, it is the rule rather than the exception, to know the exact dates of heat and breeding, and hence the expected day of parturition. In the human such information is rarely available or reliable. In the case of our patient, she had a long history of infertility, with tubal sterilization and re-anastomosis, two extrauterine pregnancies, resulting in a right-sided salpingectomy, a malformed left oviduct, possibly with adherences, although described as being patent in 1991, and 20 intrauterine inseminations which did not result in a pregnancy supported by the remaining left oviduct. This was why she was admitted for IVF treatment. After embryo transfer and before the negative pregnancy test she had intercourse once, but was not sexually active until after she was diagnosed pregnant. In addition, menstruation was not restored, she developed nausea, and
the endometrium remained in the secretory phase until an intrauterine pregnancy was demonstrated 5 weeks after embryo transfer. All of this points toward a case of delayed implantation, and not a spontaneous conception, since she did not have intercourse in the critical period.

During in-vitro cultivation, human blastocysts secrete HCG (Fishel et al., 1984), but it is only after implantation that HCG is detected in the maternal blood. A positive pregnancy test is defined by the arbitrarily chosen serum β-HCG concentration >10 IU/l. This value is significantly higher than the low basic concentration of circulating HCG (<4 IU/l) present in the serum and urine of men and non-pregnant women. HCG values >10 IU/l are usually reached 3–7 days after implantation, which in turn occurs 6–8 days after conception (Bergh and Navot, 1992; review by Chard, 1992), meaning that our patient, with an HCG value <10 IU/l on November 30, 15 days post-aspiration, should have been diagnosed as non-pregnant. With HCG values of 329 and 632 IU/l measured on January 2 and 3 (7 weeks post-aspiration), the HCG concentration could theoretically have been >10 IU/l around December 27, if a doubling time of 1.2–1.5 days was used for the calculation (Hamori et al., 1989; Pellicer et al., 1991; Bergh and Navot, 1992; Zegers-Hochschild et al., 1994). Demonstration of an intrauterine 10 mm gestation sac and a yolk sac on January 11 (8 weeks post-aspiration) corresponds with a 3.5–4 but not an 8 week old conceptus, as demonstrated by Pellicer et al. (1991), who determined the time-frames for the first detection of the embryonic sac, yolk sac and heart beats by ultrasonography in pregnancies from patients treated with IVF or artificial insemination. The two subsequent ultrasound scans on January 11 and February 24, showing crown–rump lengths of 8.1 mm (6 ± 1 weeks) and 56 mm (12 ± 1 weeks) respectively, correspond well with the previous findings.

The mechanisms behind delayed implantation are complex and differ between species, and are in general not well understood (review by Mead, 1993). Hormones, like prolactin, progesterone and oestrogen seem to be involved in the control. Sometimes the same hormone has opposite effects in two different species, which makes it impossible to extrapolate results from one species to the other. The uterus, however, plays an important role in diapause, and LIF (leukaemia inhibitory factor), which is synthesized both by the uterus and by the blastocyst, appears to be important for implantation, at least in the human and mice (Charnock-Jones et al., 1994; Stewart, 1994). A possible explanation for the delayed implantation in our patient could be the following: since no menstruation occurred after the negative HCG test 15 days post-aspiration, the corpus luteum must have been rescued. A negative HCG means that the embryo is not implanted; HCG, however, is being produced by the blastocyst, and although not systematically detectable, each of the three transferred embryos in this case should have been producing HCG, which could be triggered by a new ovulation; however, this was not demonstrated since ultrasound scans from the embryo transfer and onwards showed endometrium in the secretory phase. This case supports the findings of Edwards (1988), who reported a case in which the human implantation window was still open when three IVF embryos were replaced 1 week after the normal time for replacement, and with the uterus being in the secretory phase.

Although delayed implantation in the human has not been described before, there is no reason to believe that it does not exist. An estimate of the incidence is therefore not available. In the horse, which has an average gestation period of 336 days, with a physiological variation of 320–350 days, the incidence of extremely prolonged pregnancies (+30–63 days) has been estimated to be ~1% (Vandeplassche, 1986).

The demonstration of a pregnancy, obtained under controlled clinical circumstances and excessively prolonged by 5 weeks, as judged by HCG measurement and ultrasound scan, allows that the differential diagnosis: delayed implantation, although rare, should be considered when prolonged gestation is observed in the human.

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References


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