Superfecundation and Superfetation

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INTRODUCTION

The vast majority of human ovulations result in a monozygotic pregnancy as a consequence of fertilization of a single ovum at mid-cycle. Quite rarely, polyovulation and fertilization of more than one egg may occur, giving rise to a polyzygotic pregnancy. The true frequency of single, in contradistinction to double, ovulations is unknown, but it is accepted that there are many more multiple conceptions than multiple births. Hence, the usually quoted 0.8% of spontaneous polyzygotic multiple births is an underestimate of the frequency of polyovulation in the human female. In addition, this ratio between monozygotic and polyzygotic births is further changed because the frequency of polyovulation is much higher among women receiving ovulation-enhancing medications, and their number is not quantifiable.

Multiple ovulations may occur synchronously (at the same time) or sequentially (on different occasions during the same cycle). It follows that fertilization of more than one egg may occur during one or more inseminations (by coital acts or artificial). As a result, zygotes of different ages are created, a phenomenon known as superfecundation. The subject of superfecundation has been of interest to scholars for more than two millennia. In fact, until quite recently, the explanation of superfecundation has paralleled the theories advanced to explain the twinning process. Unfortunately, the possibility that a woman can conceive from two different coital acts, and thus potentially from two different partners, frequently led to the idea that twins were the consequence of adultery. Indeed, the association between malformations, often of the most bizarre form, and twins was explained as divine punishment for infidelity¹.

Superfecundation, defined as the fertilization of two or more ova released during the same menstrual cycle by sperm from separate acts of coitus, is frequently and erroneously confused with superfetation. In superfetation, which is an entirely different phenomenon, the fertilization and creation of another conceptus is assumed to take place when the female is already pregnant. This chapter discusses why superfetation is considered obsolete, what the evidence is for the occurrence of superfecundation in the human, and the significance of both conditions in their historical and biological context.

SUPERFETATION

In the human, progesterone, initially produced by a functioning corpus luteum and very soon later by the evolving placenta, potently up-regulates the hypothalamic–pituitary–ovarian axis to such an extent that ovulation is impossible². Spontaneous sequential ovulations are extremely rare, and can be induced by the administration of human chorionic gonadotropin but not with luteinizing hormone (LH), recombinant LH and gonadotropin-releasing hormone agonist flare-up³. Moreover, when the uterine cavity is filled by a gestational sac and the cervical mucus changes from estrogenic to progestogenic quality, there is little likelihood that sperm could enter the cervix and begin their upward journey to the oviduct. It follows that sequential ovulations in the human, occurring a few days apart, may explain superfecundation but are unable to produce superfetation.

In spite of evidence (albeit newly appreciated) to the contrary, cases of superfetation in animals and alleged cases in humans are abundant. The earliest reports came from ancient Greece, in the book of
Hippocrates entitled *On Superfetation*. Aristotle, in his *Historia Animalium*, suggested that superfetation might occur frequently in hares and mares. His observation that only humans and horses mate during pregnancy led to the assumption that superfetation is also possible in women. An extensive review of alleged superfetation cases can be found in the seminal publication of Gould and Pyle of more than a century ago. These authors cited descriptions by prominent figures such as Parè, Harvey, Mauriceau and Baudeloque. However, not everybody believed in superfetation in ancient times, as is seen in the Talmud (Nidah 27a). This passage concludes that a woman cannot become pregnant and then become pregnant again.

Alleged cases of superfetation through the ages can be explained under several categories.

**Delivery of twins of considerable discordant size (see Chapter 60).** Such cases may frequently be mistaken as being of different gestational ages rather than different sizes. For example, the Talmud describes Yehuda and Hizkiya 'who were twins, the form of one was finished to the end of the ninth, whereas the form of the other was finished to the beginning of the seventh' (Yevamot 6b). Figures 16.1 and 16.2 show a pair of discordant twins born at 32 weeks, and at the age of 2.5 years, respectively. Such twins could easily be confused with superfetation in older times.

Discordant size also occurs in cases with fetal demise when the resulting fetus papyraceus may be considerably smaller than the surviving twin, or fetuses that subsequently died in utero. Figure 16.3 shows the eight fetuses of an octuplet pregnancy spontaneously aborted at 19 weeks. This set comprises three fetuses which died spontaneously at 10–11 weeks, two fetuses that were artificially reduced and three fetuses that died during the spontaneous miscarriage at 19 weeks. In older times, the obvious size discrepancy could easily be considered as demonstrating age difference, and thus as a case of superfetation.
Additional cases of early-onset discordance (starting at < 10 weeks) have been asserted to represent superfecation. We, however, could show that very early discordance may be seen following double embryo transfer after in vitro fertilization. This explanation was not considered by the authors of references 4-6.

**Delayed interval delivery (see Chapter 75)** This refers to multiple birth occurring at different times. The literature is replete with case reports and small series of cases in which one (or more) fetus(es) was (were) aborted or delivered prematurely, whereas the remaining fetus(es) is (are) delivered days, weeks and up to several months later. Although this phenomenon may be considered (post facto) to represent superfecation, it clearly is better understood in the context of the complete history of the pregnancy.

**Fraud** As recently as 12 November 2001, the British Broadcasting Corporation reported a 20-year-old Italian woman who had not used any fertility drugs, and claimed that she was going to deliver a singleton that week and then again 3 months later (of triplets). The case became doubtful when the baby was not born in November, and when the would-be father claimed that his wife delivered the first baby, vaginally, sometime in December. Eventually, in January 2002, the woman admitted that she was never pregnant, explaining: 'We tried fertilization treatment that went wrong. But then we invented the story about the double pregnancy, and weren't able to stop it.'

Interested readers may be amused to read the story reported by a prestigious medium. Whereas one may wonder how such a fraud could reach international proportions in the 21st century, one should admit that shamms related to twinning are still possible.

**Misdiagnosis of a multiple pregnancy** Before the advent of ultrasonography, twins were frequently diagnosed at birth, following the delivery of twin A. Transabdominal sonography enabled the early diagnosis of twins; however, the rate of missing one sac – especially in high-order multiples – was higher than that noted following the introduction of transvaginal sonography. It is possible that in some cases, in which one sac was initially visualized and a second sac appeared on a subsequent scan, an erroneous impression of superfecation arose.

As noted above, the scientific arguments used to discard the hypothetical occurrence of superfecation are the arrest of further ovulation after the initial ovulation and the inability of sperm to reach the fertilization site in the Fallopian tube. However, modern infertility treatment can theoretically circumvent these obstacles in one of two manners. The first is transfer of sperm directly to the Fallopian tube by a procedure called gamete intrafallopian transfer (GIFT). If this procedure is performed when the patient is already pregnant, and follicles are pushed to ovulate under the influence of hCG, a 'retrograde' fertilization may occur. Obviously, such a gestation is likely to develop in the Fallopian tube because the preceding gestational sac blocks the uterine cavity. A second possibility arises from the fertilization of oocytes in vitro, a routine procedure in assisted reproductive technologies. Once created in vitro, zygote transfer directly to the Fallopian tube by a procedure called zygote intrafallopian transfer (ZIFT) performed inadvertently during an early gestation may create a heterotopic superfecation.

The ovulatory-inhibitory effect of an intrauterine pregnancy might not be the same in the presence of an extrauterine pregnancy. It is speculated that the latter produces less progesterone because of less trophoblastic tissue and a diminished effect on the corpus luteum. It is therefore possible that, in such circumstances, an ovarian follicle might escape the progesterone-induced ovarian suppression. This may be the reason why heterotopic superfecations are repeatedly mentioned in the older as well as in the more recent literature.

In summary, superfecation should be considered under the following possibilities:

1. As a misnomer, describing, in fact, superfecation;
2. As an erroneous diagnosis of other conditions;
3. In the circumstance of a heterotopic pregnancy;
4. In the case of GIFT or ZIFT performed during an ongoing early pregnancy.

**SUPERFECUDATION**

Superfecudation is also known from ancient times. Aristotle discussed this condition in relation to the Greek mythology of Leda, the wife of Tyndareus, King of Sparta. Leda was seduced by Zeus – king of the gods – who disguised himself as a swan. After Zeus impregnated her, her husband impregnated her again. Eventually, she laid two eggs, each producing unlike-sexed twins: Pollux and Helen – the children of Zeus – emerged from one egg, and Castor and Clytemnestra – the children of Tyndareus – from the other.

This erotic mythology provoked the imagination of innumerable artists. My first choice of the two best examples is the 1924 poem describing the mating of Leda and Zeus by William Butler Yeats (Table 16.1). My second best is Leonardo da Vinci's painting of *Leda and the Swan*. The copy shown in Figure 16.4 is one of two done by pupils of the master after the original painting was burned. Of note is the gross mistake showing unlike-sexed twins hatching from a single egg. It
and Pyle described the case of a mare that was impregnated sequentially by a stallion and an ass, and eventually delivered at one parturition a horse and a mule. In the human, the best examples are those in which the twins born to the same woman are of different colors. Gould and Pyle cited a long list of prominent medical authorities that described such cases, the earliest of which was from 1714. Interestingly, most cases in the past, but certainly not all of them, described black women (many of whom were servants) who acknowledged that shortly after being with their respective husbands, they had intercourse with a white man.

A mix-up at a Leeds in vitro fertilization (IVF) clinic in 2002 resulted in the delivery of twins of different colors to an infertile white patient. The blunder could have been at either the fertilization stage (using sperm of a different father, i.e. heteropaternal pregnancy) or the embryo transfer stage (using an embryo from a different couple, i.e. heterologous pregnancy). DNA fingerprinting confirmed the former possibility. However, in its 'pure' sense, these heteropaternal twins were not a result of superfecundation because they were produced by inseminating retrieved eggs of the same ovulation cohort. Interestingly, England's senior family judge, Dame Elizabeth Butler-Sloss, ruled that the biological father was also the legal father of the twin; however, Dame Elizabeth suggested that the rights of the non-biological father could be protected by court adoption order.

Heteropaternal superfecundation seems to be an anecdotal and rare occurrence; however, Wenk and colleagues identified three cases in a parentage-test database of 39,000 records and quoted a frequency of 2.4% heteropaternal superfecundations among dizygotic twins whose parents were involved in paternity suits. James suggested that about one pair in 400 is heteropaternal in the population of dizygotic twins born to married white women in the USA. The incidence of heteropaternal superfecundation, however, clearly depends on rates of infidelity in the population, and may be substantially higher in small selected groups of dizygotic twin maternities, such as women engaged in prostitution. The frequency of twins with different fathers also depends on the extent of efforts in performing elaborate genetic analyses, leading to the impression that the frequency of heteropaternal superfecundation is underestimated, at least in selected populations.

Superfecundation is by no means equivalent to heteropaternity. Estimates from the Galton Institute in London suggest that at least one dizygotic twin maternity in 12 is preceded by superfecundation, with varying frequencies depending on the population's coital rates and rates of double ovulation. Monopaternal superfecundation may also occur in assisted reproduction. Amsalem and colleagues

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**Table 16.1** *Leda and the Swan* by W.B. Yeats (1924)

A sudden blow: the great wings beating still
Above the staggering girl, her thighs caressed
By the dark webs, her nape caught in his bill,
He holds her helpless breast upon his breast.
How can those terrified vague fingers push
The feathered glory from her loosening thighs?
And how can body, laid in that white rush,
But feel the strange heart beating where it lies?
A shudder in the loins engenders there
The broken wall, the burning roof and tower
And Agamemnon dead.
Being so caught up,
So mastered by the brute blood of the air,
Did she put on his knowledge with his power
Before the indifferent beak could let her drop?

**Figure 16.4** *Leda and the Swan* by Leonardo da Vinci (c. 1505-10): oil on wood. Reproduced by kind permission of the Earl of Pembroke, Wilton House, Salisbury, UK

Could be that Leonardo followed the mythology verbatim, or that zygosity was totally unknown at that time.

The diagnosis of superfecundation is often conjectured and speculative. On the other hand, the diagnosis of superfecundation, especially the heteropaternal pregnancy – when the twins are of different color or racial phenotype – is usually unquestionable. Gould
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reported the transfer of two embryos on day 3 and the development of five separate embryonic sacs. Genetic analysis of the twin pregnancy and of the three embryos that were reduced confirmed monopaternal superfecundation. IVF patients with patent Fallopian tubes should be cautioned against intercourse late in their controlled ovarian stimulation, especially if they would decline multifetal reduction.  

ETIOLOGY AND BIOLOGICAL SIGNIFICANCE OF SUPERFECUNDATION

There is no convincing explanation of why superfecundation occurs, and if it occurs why it is an exceptional phenomenon. With our current understanding of the ovulatory mechanism, some of the theories offered in the past seem outdated. In general, spontaneous or induced sequential ovulations are unable to produce superfecundation unless met by timely insemination. It follows that sequential fertilizations depend on either the viability of sperm in the female genital tract, or multiple inseminations (natural, artificial or both). Natural multiple inseminations within the time period of potential fertilization means an increased coital frequency at this period. James pioneered the proposition of high coital frequencies at the time of conception related to the birth of dizygotic twins. In simple terms, this means that fertilization of the second egg of a double ovulation is more likely to be achieved by frequent ejaculations. It was estimated that if the coital rate of young women is doubled, their dizygotic twin probability is increased by roughly 25–30%.  

This theory was not substantiated by Danish data, which found similar coital frequencies in parents of twins and parents of singleton infants, but was indirectly supported by Swiss data analyzed by Eriksson and Fellman, who deduced that the seasonality of coital rates paralleled variations of coital rates and multiple ovulation in the early summer months. Another link between superfecundation and coital frequency comes from the alleged increase in gonadotropin levels arising from the erotic response to coitus, which is indirectly mediated by the erotic response to coitus.  

The biological significance of superfecundation is largely unknown. This is primarily related to the underestimation of its occurrence in fertile monogamous couples. In addition, the interval between two or more sequential fertilizations may be within the range of a few days or less, a time difference that is insufficient to show distinguishable discordances in multiple pregnancies. Regardless, the saga of superfecundation is being revived in recent years, with application of modern technology to understand this phenomenon. It is possible that the very early zygote and its hormonal production may affect in some way the development of a second, younger, zygote. It is unknown, however, whether this effect is beneficial or detrimental to the multiple pregnancy.

REFERENCES

13. http://guardian.co.uk/uk_news/story/0,3604,903777,00.html  