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Monochorionic diamniotic dizygotic twin pregnancy

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SUMMARY

Recently, the obstetric mantra that "monochorionicity guarantees monozygosity" has been finally overthrown. It has been proven that monochorionic diamniotic dizygotic (MCDADZ) twin pregnancies, sharing the same placenta, do occur, though very rarely. Also in dizygotic twin pregnancies vascular connections may develop between foetuses. Thus, in the twin-to-twin transfusion syndrome (TTTS) and in conjoined twins in certain cases foetuses may differ genetically or even be of different sex. This paper analyses possible mechanisms leading to the development of monochorionic diamniotic dizygotic twin pregnancy on a basis of the latest studies.

Keywords: monochorionic diamniotic dizygotic twin pregnancy, aetiology

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INTRODUCTION

There is a commonly accepted doctrine in the medicine that monochorionic [MC] twins are always monozygotic [MZ]. This doctrine was based on two studies covering 800 pairs of MC twins, in which macroscopic and microscopic pictures of a placenta were compared to zygosity diagnosed by determination of serological blood markers [1,2]. However, differences in cytogenetic and pathological tests occurring in some cases in MC twins questioned reliability of this reasoning [3]. Recently, the obstetric mantra that "monochorionicity guarantees monozygosity" has been finally overthrown. It has been proven that monochorionic diamniotic dizygotic (MCDADZ) twin pregnancies, sharing the same placenta and blood circulation, do occur, though very rarely. In majority of described cases, these twins resulted from artificial methods of procreation (ART.), and microinjection techniques in particular [4,5]. Recently, six cases of spontaneous MCDADZ twin pregnancies were described. They occurred after previous hormonal stimulation of ovaries [6–11]. Unfortunately, only in two cases the diagnose was unambiguously confirmed by histological and genetic tests [6,7].

AETIOLOGY

It appears that in natural circumstances, spontaneous MCDADZ twin pregnancy may develop when:

- blastocysts are implanted in uterus close to each other;
- oocytes without a zona pellucida are present;
- biovular Graafian follicles are present;
- spontaneous division of the ovum even before its fertilisation by two sperms (parthenogenetic division).

One of the options for development of a shared placenta in dizygotic twins (MCDADZ pregnancy) may be an accidental implanting of blastocysts close to each other and their accidental fusion within trophoblasts. Nylander

and Osunkoya [12] were the first to indicate such possibility, when in 1970 they described a case of a pair of twins of phenotypically different sex, but with MCDA foetal membranes, as confirmed by a histopathological test. They proposed that during the early stages of pregnancy initially separate chorions had to fuse and the dichorionic pregnancy with fused placentas developed, and then chorionic tissues within the separating septum degenerated and the monochorionic pregnancy eventually developed. Although this mechanism cannot be wholly excluded, in the case described by Souter VL et al., [5], histological tests and in situ hybridisation did not find any chorionic residues within the separating septa in, only a presence of closely located amniotic membranes.

Another aetiological factor may be a situation where trophoblasts belonging to two genetically different blastocysts fuse spontaneously even before their implanting into the uterine wall. In consequence, two genetically different, non-chimeric cells of an inner cell mass start to develop into a single membrane formed by chimeric trophoblast cells. This option was supported by tests in animals which showed that in mammals pre-implantation fusion of embryos may occur in in vitro conditions [13].

In the IVF offices, oocytes without a zona pellucida are frequently observed. This concerns ova collected directly from the Graafian follicles, as well as following previous manipulations within their zona pellucida or after incubation in the culture media [1–3,14].

In natural conditions, primary absence of zona pellucida is usually caused by disorders in the process of its development. In 1999, Ding et al. were one of the first to report two cases of oocytes without zona pellucida which was possibly iatrogenically removed when the cell was collected from the cumulus oophorus (following previous administration of the hyaluronidase solution) [1]. These cells were later successfully fertilised. Shu et al. also noted two cases of successful fertilisation of frozen and then thawed embryos without zona pellucida [2]. It was removed during oocyte aspiration from the cumulus oophorus. Hiroaka et al. were the first to describe a full-term pregnancy resulting from a transfer into the uterus of thawed blastocyst, in which secondary atrophy of zona pellucida occurred during culture [3]. Stranger et al., on the other hand, described a pregnancy from the ICSI procedure applied in a woman whose oocytes were originally devoid of zona pellucida following disorders in its development [14].

In natural conditions, oocytes in Graaphian follicles, even zona-free ones, are usually surrounded by the corona radiata. Therefore, they can be recognised only after their collection or during the ICSI procedure. Because their appearance is abnormal and they represent only a small percentage of collected ova, they are usually eliminated from further fertilisation procedures. However, the problem occurs when all ova collected from a given woman are zona-free. The current progress in fertilisation techniques allows to fertilise them. Unfortunately, in most cases they are damaged and die at early stages of their development. First live births of children from pregnancies resulting from fertilisation of such oocytes were noted in 2010 [2]. These pregnancies resulted from a transfer of thawed blastocysts from oocytes with iatrogenically removed zone, during manipulations within *zona pellucida* and *corona radiata*. In 2016, the first case of a live birth of twins born in 38 gestational week, who developed from ova spontaneously (naturally) free of the zona, was described. In that woman all collected oocytes were without zona pellucida. The pregnancy developed after these cells were fertilised using the IVF-ICSI method, and fresh, unfrozen blastocyts were transferred [15].

Another option for development of MCDADZ pregnancy concerns a case when two ova that developed in the same oocyte within the same zona pellucida are fertilised by two sperms, and then their trophoblasts are fused before hatching. For a long time already, a presence of Graafian follicles containing two ova was observed in surgically removed ovaries, and they could be a potential source of twin pregnancies. However, Gougeon et al., studying a group of women in which this type of Graafian follicles were found, did not observe a higher frequency of multifoetal pregnancies in them [16]. Furthermore, in most cases these ovaries were removed during post-ovulation phase of the cycle. They concluded that ability of such ova to ovulate appeared to be reduced, and a possibility of twins' development was uncertain. This theory was forgotten for many years. That mechanism for development of twin pregnancies was brought to attention again when biovular Graafian follicles were found in ovarian aspirates collected for "in vitro" fertilisation. Such follicles were found in 15 (0.3%) out of 4,695 collected ova [17]. Zeilmaker [18] and other authors [19,20] demonstrated that ova of

this type can not only be fertilised in laboratory conditions, but they can also develop to a stage of at least 8 blastomeres. Furthermore, embryos developing from biovular Graafian follicles started to develop within the same zona pellucida. This direct contact of two different blastocyts can, at least in theory, lead to their fusion. This would explain some very surprising and difficult to interpret foetal development anomalies, including MCDADZ twin pregnancies, chimeras involving cells of the whole body (a tetragametic chimera - an organism consisting of a population of two genetically different cells originating from separate zygotes) or conjoined twins of different sex [21]. Therefore, it cannot be excluded that this way of development of monochorionic dizygotic twins is more common than currently assumed. However, it has not yet been finally confirmed whether both zygotes can develop in a normal twin pregnancy.

Another explanation for development of the MCDADZ twin pregnancy may be a situation in which the parthenogenetic division of the ovum occurs even before it is fertilised by two sperms [22]. The experimental in vitro studies shown that the parthenogenetic division of human oocytes is possible. Indirect evidence confirming that concept was provided by analyses of DNA markers in people with complete chimerism [18,19]. A fusion of chorions and development of a monochorionic placenta may result in a development in a placenta of vascular anastomoses and blood circulation shared by DZ twins. This will cause a well-documented blood chimerism present in erythrocytes and leukocytes [25–27]. It is also possible that transfusion of germline stem cells occurs resulting in chimerism of germ cells. In consequence, in female twins each woman can produce gametes genetically belonging to her twin. Thus, from the genetic point of view, she cannot be a biological mother of children born to her. In the MCDZ female and male pair, consequences to female twins can be even more serious, with virilisation developing in a woman caused by hormones of her male twin, and resulting in infertility [28]. At least in theory, changes being an equivalent of cattle "*freemartinism*" can develop in a girl. To this date, this situation has not been confirmed in humans. "Freemartins" are sterile cows that had a male twin during their development in the uterus. This condition is caused by formation of vascular connections between foetuses in a dichorionic placenta and a transfer of male hormones to female body through them. Freemartins are also called "false" cows, because they will never become fertile and will never give milk. Their name comes from St. Martin, because in England they were considered worthless and traditionally killed on St. Martin's Day (St. Martin's steak).

Methods of assisted procreation, particularly those associated with microinjection techniques, may result in a rupture of zona pellucida during the zygote passage through fallopian tubes and in a secondary complete or partial fusion of separately developing embryos. When two DZ embryos fuse completely, a tetragametic chimera develops. On the other hand, when only embryonic trophoblasts fuse before implanting in the uterine wall, then a shared chimeric chorion (and then placenta) is formed, inside which two normal DZ embryos, initially originating from separate cells of the inner cell mass, will develop [5]. This will result in the monochorionic diamniotic dizygotic (MCDADZ) twin pregnancy.

CONCLUSION

Concluding, in exceptional circumstances, even, when twins are dizygotic (of different phenotype, including different sex), they can be MC and share the placenta and blood circulation. In dizygotic twin pregnancies with monochorionic placenta, an immunological tolerance possibly exists between twins. This is of a great importance when any organ transplant must be performed between siblings.

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