

# THE EPIDEMIC OF TWINS: THE CHALLENGE IN OBSTETRICS AND GYNAECOLOGY

\*Ernesto González-Mesa,<sup>1</sup> Olga Cazorla,<sup>2</sup>  
María José González-Valenzuela<sup>2</sup>

1. Department of Obstetrics and Gynecology, University of Málaga, Málaga, Spain

2. Department of Evolutionary and Educational Psychology, University of Málaga, Málaga, Spain

\*Correspondence to [egonzalezmesa@gmail.com](mailto:egonzalezmesa@gmail.com)

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## ABSTRACT

In the past 50 years, the incidence of multiple pregnancy has increased dramatically due almost exclusively to two factors: delayed childbearing and assisted reproduction techniques (ARTs). Although the clinical guidelines and protocols currently endorsed by scientific societies have systematised the obstetric care required in multiple pregnancy, the effects of obstetric care beyond the perinatal period have seldom been evaluated. Twin deliveries also involve additional difficulties derived from the need for 'simultaneous' care of two fetuses during the expulsive period, during which the second twin is particularly vulnerable due to potential complications. Chorionicity, gestational age at birth, ART, birth order, and some parental variables, such as maternal age, have been studied as possible sources of neurodevelopmental delay in twins.

**Keywords:** Multiple pregnancy, assisted reproduction, perinatal outcomes, preterm birth.

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## MULTIPLE PREGNANCY

Simultaneous development of two or more fetuses in the uterus is a normal phenomenon in lower mammals but is rare in humans. Evolutionary adaptation of the maternal organism is aimed at developing a single fetus. Therefore, multiple pregnancy, though not strictly pathological, represents a deviation from the norm and, to some extent, a phylogenetic regression. If we consider that the first hominid species with human reproduction patterns appeared 2.5 million years ago, then we can assume that the increased number of multifetal pregnancies observed in the last 50 years will carry a biological price. In this sense, Keith<sup>1</sup> wondered 30 years ago whether the maternal and neonatal risks posed by iatrogenic multiple pregnancy were justified.

Multiple pregnancy increases first trimester symptoms such as nausea, headache, dizziness, and cramps, while hyperemesis gravidarum, threatened abortion, gestational hypertension, gestational diabetes, anaemia, venous insufficiency, and sciatic pains are more frequent. Hypervolume in

the final months produces palpitations, persistent constipation and frequent urination, oedema and vascular compression in the legs and vulva, and dyspnoea. Maternal weight gain in multiple pregnancy is higher than in singleton pregnancy, approximately 20 kg.<sup>2</sup>

The risk of maternal complications such as preeclampsia, diabetes, premature rupture of membranes, and anaemia increases with the number of fetuses.<sup>3,4</sup> In addition, the risk of maternal death is 3.6-times higher in multiple gestations (plurality-specific pregnancy mortality ratio: 20.8 deaths per 100,000 multifetal pregnancies versus 5.8 deaths per 100,000 singleton pregnancies) independent of race and socio-cultural status.<sup>5</sup> From a psychological point of view, multiple births are also a source of destabilisation and social disruption in relationships. Such situations cause stress, depression, and frequent mood swings. The studies published to date suggest that these problems are present in one of every three or four families. Postpartum depression is 40% more likely in cases of multiple pregnancy.<sup>6</sup>

The most common complication of multifetal pregnancy is preterm birth.<sup>7</sup> Birth occurs before 37 weeks in 50% of twin pregnancies and in 99% of triple pregnancies, which results in perinatal morbidity and mortality. The risk of cerebral palsy is four-times higher in twins than in single births.<sup>8</sup> The probability of dying in the first year of life due to prematurity is seven-times higher in the case of twin pregnancies, and the proportion with low birth weight is up to seven-times higher.

## CAUSES

During the past 50 years, the incidence of multiple pregnancy has increased due almost exclusively to two factors: delayed childbearing and assisted reproduction techniques (ARTs).<sup>9,10</sup> Age is considered an independent risk factor for natural multiple pregnancy.<sup>11</sup> The probability of conceiving more than one fetus increases between the age of 35-39 years and declines thereafter, except among the black population in whom an increasing trend is observed after this age.<sup>12</sup> In these populations, higher levels of endogenous follicle-stimulating hormone (FSH) cause multiple ovulations and, consequently, multiple pregnancies.

On the other hand, ARTs are the only possibility of conceiving for some women, and so treatments in assisted reproduction centres include high doses of FSH to allow the development of more than one egg per cycle, or intrauterine transfer of more than one embryo simultaneously, in order to increase the chances of pregnancy during a cycle of ovarian stimulation. Results of ART are very often evaluated only in terms of implantation rates and pregnancy rates per cycle, and ignore everything related to pregnancy and multiple birth complications, prematurity of newborns, or the economic or psychological overload that appears when more than one child is delivered.

The role of ART as the primary aetiological factor for multiple pregnancy is clear, as is the interest of fertility centres in preventing its occurrence. Commercial interest in private centres and the economic interest of the pharmaceutical industry make it very difficult to consider the biological, economic, social, and psychological costs relating to multiple pregnancies, transferring multiple embryos, and hyperstimulating ovarian cycles.<sup>13</sup> Given the extraordinary consequences of these procedures and the lack of communication between ART specialists and obstetricians, medical societies should promote new regulations. When

a multiple pregnancy is detected, the obstetrician is usually the one who has to warn the future parents about the physical, social, psychological, and economic consequences. However, accurate information should be provided to women prior to ART. Actions such as the official promotion of single-embryo transfer or the compulsory and systematic registration of final perinatal outcomes after ART performed in fertility centres should be taken into account.

## OBSTETRIC VARIABLES AND LONG-TERM OUTCOMES IN TWINS

Psychoevolutionary development, skill acquisition, behaviour, and school achievement are subject to the influence of a number of variables. Some of these variables, which affect the perinatal period, have often been associated with a poor outcome. On the other hand, the increasing number of multiple pregnancies in recent years has raised a particular concern about the problems associated with such pregnancies in terms of prematurity and adverse perinatal outcomes.

It should be noted that although the scientific literature is riddled with studies conducted in twins, most of them stem from the paradigm of medicine and 'differential psychology' introduced by Galton in the 19<sup>th</sup> century.<sup>14</sup> This scientist delved into the debate between the innate and the acquired, and focussed on ascertaining the impact of heredity and environment on certain health traits. A smaller number of studies in twins report that these children are a unique population group with particular needs and an intrinsic complexity amenable to specific clinical, social, and educational research. Although the clinical guidelines and protocols currently endorsed by scientific societies have systematised the obstetric care required in this type of pregnancy, the effects of obstetric care beyond the perinatal period have seldom been evaluated. Most of these guidelines are based on expert recommendations rather than randomised studies.<sup>5</sup>

It is worth mentioning that pregnancy risks, clinical management, and subsequent outcomes are very different for monochorionic and dichorionic twin pregnancies. Therefore, determination of chorionicity is required in order to correctly stratify perinatal risk according to the type of twin pregnancy. Even the duration of the multiple pregnancy depends on chorionicity. On the one hand, women with monochorionic,

uncomplicated twin pregnancies should know that elective birth from 36 weeks and 0 days does not appear to be associated with an increased risk of serious adverse outcomes, and that continuing uncomplicated twin pregnancies beyond 38 weeks and 0 days increases the risk of fetal death. On the other hand, women with dichorionic, uncomplicated twin pregnancies should be aware that elective birth from 37 weeks and 0 days does not appear to be associated with an increased risk of serious adverse outcomes, and that continuing uncomplicated twin pregnancies beyond 38 weeks and 0 days increases the risk of fetal death.

Delivery of twins involves additional difficulties derived from the need for 'simultaneous' care of two fetuses during the expulsive period, during which the second twin is particularly vulnerable due to potential complications. In this regard, we believe that it has not been adequately evaluated whether twin deliveries, as currently performed, provide the same chances to both fetuses and whether this has any impact on subsequent stages of development.<sup>15</sup> It is very difficult to define the period in which obstetric variables started to be considered important for normal neuropsychological development in children. As early as 1955, Pasamanick and Lilienfeld<sup>16</sup> demonstrated an association between some maternal and fetal factors and delayed child development, and postulated the hypothesis of the 'continuum of reproductive casualty'. The observed relationship between certain neuropsychological disorders and some obstetric complications, such as placenta previa or obstructed, multiple, or premature delivery, led these authors to hypothesise the existence of a continuum of casualty in which an extreme of severe, lethal fetal involvement (cases of abortion and fetal or perinatal death) and a number of other conditions that involve sublethal damage, possibly including cases of cerebral palsy, epilepsy, mental retardation, learning and developmental difficulties, and behavioural disorders, could be recognised. Many studies have subsequently been able to document the existence of neurological and cognitive development problems in children exposed to obstetric and perinatal risks such as prematurity, low birth weight, and perinatal hypoxia;<sup>17</sup> one study has demonstrated that, even when these children have apparently normal psychometric results, there are often learning difficulties and special educational needs.<sup>18</sup> It should be taken into account that any association between prematurity

and psychological development may be due to the causes of prematurity rather than to prematurity itself.<sup>19</sup>

Because a significant growth in brain mass occurs during the final weeks of gestation, during which corticomedullary differentiation processes are also completed, the risk of impaired neurological and cognitive development is greater in late preterm infants compared with term infants.<sup>20</sup> Behavioural problems,<sup>21</sup> neurodevelopmental delay, and difficulty acquiring reading skills<sup>22,23</sup> have been reported. In agreement with these studies conducted in single pregnancies, a statistically significant correlation between twins' gestational age at birth and intelligence quotient scores at 6 years of life has been reported. In addition, scores were systematically higher in children born beyond 37 weeks of gestational age in all school achievement areas evaluated.

In some studies, the use of ART has been associated with the occurrence of neurodevelopmental delay in children.<sup>24</sup> Although results are conflicting, assisted reproduction protocols do not appear to be associated with severe cognitive impairment or significant neurodevelopmental delay, but their potential relationship to mild delay or impairment should be investigated.<sup>25</sup> Because one of the most common complications of ART is the high multiple pregnancy rate, assessment of the impact of these techniques on academic achievement, intelligence, and neuropsychological maturity areas in twins is of special interest.

Various studies have associated advanced maternal age with better academic achievement<sup>26</sup> and better scores in the neurocognitive evaluation of children.<sup>27</sup> Some authors<sup>28</sup> suggest that this association is mediated by the existence of favourable social and familial determinant factors associated with advanced maternal age, which allow for child development in a more educational and stable environment. The differences between children born first and second according to the type of delivery have also been investigated. Some authors have reported a greater risk of perinatal morbidity in vaginal delivery of the second twin.<sup>29-32</sup> Other studies, however, could not show any benefit of elective caesarean section over vaginal delivery of the second twin.<sup>33-35</sup> It appears difficult to reach conclusions in this regard. While delivery by caesarean section prevents a poorer score in development areas for the second-born twin, the

impact of the type of delivery can vary with regard to academic achievement, neuropsychological development, and intelligence. It was revealed that vaginal delivery was associated with better scores in the areas of reading accuracy, total reading, phonetic orthography, visual orthography, calculation, writing, articulatory language, expressive language, spatial structuring, visual perception, non-verbal development, and matrices. Based on these results, vaginal delivery appears to be the most advantageous option.

Twin delivery, however, involves a certain hierarchy in birth conditions so that, although vaginal delivery is globally associated with better results in the reported areas, when the hierarchy involved in birth order is introduced then circumstances where the second twin benefits from delivery by caesarean section are detected. Published results<sup>32</sup> suggest a disadvantage to the second twin, with the differences in the perinatal period noted by

other authors<sup>36-38</sup> possibly being reflected at school age. At this point in time, management of the risks and interests of each infant and the mother should be thoroughly agreed upon.

Multiple pregnancy is a source of medical complications for mothers and newborns. Long-term effects on child development are not negligible, are a source of psychological maladjustment and destabilisation of the family, and generate a significant economic burden. The economic cost of a multiple pregnancy may be 10-30-times the cost of a single *in vitro* fertilisation cycle, which is the main aetiological factor. The increase in multiple pregnancies can be described in terms of an epidemiological health alert. It is necessary to develop clinical protocols for single-embryo transfer and legislative tools in order to reduce maternal morbidity, perinatal mortality, and disability resulting from the prematurity caused by multiple births.

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