

THE EAST FLANDERS PROSPECTIVE TWIN SURVEY (EFPTS) : 55 YEARS LATER

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Abstract

The East Flanders Prospective Twin Survey (EFPTS) is a registry of multiple births in the province of East-Flanders, Belgium. Since its start in 1964 over 10,000 twin pairs have been registered. EFPTS has several unique features: it is population-based and prospective, with the possibility of long-term follow-up; the twins (and higher order multiple births) are recruited at birth; basic perinatal data are recorded; chorion type and zygosity are established; and since 1969 placental biopsies have been taken and frozen at -20°C for future research. The EFPTS includes since its origin placental data and allows differentiation of three subtypes of monozygotic (MZ) twins based on the time of the initial zygotic division: the dichorionic-diamnionic pairs (early, with splitting before the fourth day after fertilisation), the monochorionic-diamnionic pairs (intermediate, splitting between the fourth and the seventh day post fertilisation), and the monochorionic-monoamnionic pairs (late, splitting after the eighth day post fertilisation). Studies can be initiated taking into account primary biases, those originating "in utero". Such studies could throw new light on the consequences of early embryological events and the gene-environment interactions as far as periconceptual and intrauterine environment are concerned.

Introduction

The East Flanders Prospective Twin Survey (EFPTS) was started in July 1964 at Ghent University, Department of Obstetrics, by Robert Derom and Michel Thiery, a twin himself. At present it is hosted in "Twins", a non-profit Association for Scientific Research in Multiple Births and is now partly funded by the University of Ghent (Belgium), "Twins" and the University of Maastricht (the Netherlands).

Fifty five years later EFPTS is still active with current research conducted in close collaboration with the Centre for Environmental Sciences of Hasselt University (Belgium) and the departments of Psychiatry and Neuropsychology and Complex Genetics of Maastricht University (the Netherlands).

The main aims of EFPTS are:

- (1) the determination of the prevalence of multiple births in a well defined geographic area and the recording of the obstetrical (duration of pregnancy, pregnancy and birth complications, birth weight, induction of ovulation, placental weight, insertion of the

cord, etc.) and obstetrico-pediatric outcomes (intra-uterine growth, congenital malformations, perinatal and infant morbidity and mortality, etc.);

(2) the investigation of the causes of the multiple pregnancy and the origin of twinning;

(3) the influence of the prenatal environment on the investigated traits on later age such as behaviour, learning- and school problems, intelligence, postnatal somatic growth, sexual maturation, blood pressure, stress, (sub)clinical depression and psychotic symptoms etc. Understanding how the perinatal period shapes the human epigenome and which genomic regions are sensitive to environmental influences will allow us to distinguish a healthy start of a new life from an unfavourable start;
and

(4) the determination of the genetic predisposition of the investigated phenotypes and the role of the environment (with special emphasis on the prenatal environment) both individual-specific as well as common environmental influences.

Sample characteristics

The inclusion criteria are the following: all multiple births in the Province of East Flanders, Belgium (14,000 births per year) from whom at least one of the children, live- or stillborn, weights 500 g or more or, when birth weights are unknown, the gestational age is at least 22 weeks. The specific methodology of this survey includes: the determination of the zygosity of each multiple birth with near certainty to certainty through examination of the placental membranes and vascular anastomoses, blood groups and DNA fingerprints (if necessary), the collection of medical data from gynaecologists and neonatologists, follow-up of the multiples through one of the studies and/or questionnaires.

Contact with the families of the multiples is maintained by an annual newsletter, a TWIN hotline for the public and the parents of twins with psychological, educational, medical or practical problems and the organisation of different evening meetings 4 times a year . These services to families with multiple births is a joint venture of EFPTS and the Association for Scientific Research in Multiple Births (Twins) and is mainly based on the work of volunteers. The newsletters are published on the EFPTS website (www.twins.be) and more recently Facebook was started to share information on a more informal level.

The EFPTS respects the privacy of all future participants (parents and children) in accordance with the Belgian law of 22 August 2002 on patient rights and the General Data Protection Regulation

(or GDPR) (EU) 2016/679 of 27 April 2016. Therefore, the registry protocol will be submitted in 2019 to the ethical committee of all participating hospitals in East Flanders. Ghent University hospital will act as the coordinating center. This change means that an informed consent needs to be signed by all future mothers, to confirm her acceptance of the registration of the obstetrico-pediatric data and the collection of a biopsy of the placenta.

Between 1964 and 2019 more than 10.000 twin pairs and 250 triplet sets were registered and investigated (see table 1). The EFPTS sample is representative of the total twin population of East Flanders with more than 95% registered multiple births since 1990 (Loos et al., 1998). Presently more than 3000 twin pairs have been enrolled in more than 10 major follow up studies. Table 2 gives an overview of the most important follow-up cohorts of the registry.

Insert here table 1 and table 2

EFPTS findings

The main aim of the Developmental Origin of Health and disease (DOHaD) hypothesis is to link early life risk factors with specific chronic diseases, including those of cardiovascular and neurodevelopmental nature. As early life risk factors can originate during gestation, EFPTS is ideally designed to identify some of these risk factors. The storage of placental tissue for decades and the access to birth addresses of all registered twins and triplets gives us the opportunity to retrospectively study factors such as birth weight, preterm birth and the maternal exposure to ambient air pollutants as causal risk factors for different (sub)clinical phenotypes. Stored placental biopsies allow us furthermore to look at molecular markers such as telomere length, mitochondrial DNA content and genome wide methylation patterns in association with these different phenotypes.

To further illustrate the scope of our studies some of the most important results are reported.

Perinatal outcome and timing of twinning

- The MZ monochorionic-monoamnionic (MC-MA) twin pairs are predominantly girls (Derom et al., 1988). The MZ monochorionic-diamnionic (MC-DA) twin pairs have a higher mortality rate than DC MZ and DZ twin pairs. If the division takes place after the 8th day, the mortality risk increases even more dramatically (Loos et al., 1998).

- After standardization for gestational age, the birth weight of twins is mainly determined by maternal factors especially the mother's genetic make-up, and to a lesser extent by the chorion type and the genes of the foetuses and their common environment (Vlietinck et al., 1989).
- Since the mid 1980s there is a real explosion in the rate of multiple births, primarily caused by the increasing administration of ovulation stimulating agents and the use of other assisted reproduction techniques (ART). EFPTS was the first to draw attention to the importance of this epidemic. This increase in the rate of multiple pregnancies represents an important public health problem because of the rate of very preterm births and very-low-birth weight infants in the twin population (Derom et al., 1993). More recently there has been a steep decrease of the rate of higher order multiple births and twins, because of a selective feticide (selective abortion of one or more embryos or fetuses) policy and the single embryo transfer in in vitro fertilisation (IVF) (De Neubourg & Gerris, 2003).
- The frequency of zygotic splitting is higher after artificial induction of ovulation than after naturally occurring ovulation, which is of fundamental unexplained biological importance (Deromet et al., 1987). Among iatrogenic MZ twins, the ratio of MC to DC pairs is higher compared with spontaneous twins. A greater proportion of MZ twins is observed with clomiphene citrate as the sole treatment compared with other ovulatory drugs (Derom et al., 2006).
- The assumption that the division of the zygote occurs stepwise later in respectively DC-MZ, MC-DA and MC-MA pairs, has been demonstrated to be highly probable by studying X-inactivation within MZ female pairs: X-inactivation is totally symmetrical in MC-MA pairs, almost symmetrical in MC-DA pairs and asymmetrical in DC-MZ pairs (Chitnis et al., 1999; Monteiro et al., 1998).
- The belief that discordant handedness in MZ twins represents mirror-imaging is mythical: the often observed higher frequency of left-handedness in twins is confirmed but seems to be independent of zygosity and chorion type (Derom et al., 1996).
- In unlike-sexed twins the length of gestation and the birth weight of the male co-twin is influenced by his female co-twin and not the other way around (Loos et al., 2001a).
- Twins conceived through ovulation induction, IVF or intracellular sperm injection (ICSI) are at significantly elevated risk of preterm birth and, to lesser extent, of low birth weight. The observed risks associated with assisted reproduction are dampening down by predominantly

dizygotic twinning following assisted reproduction and by differential maternal characteristics (Verstraelen et al., 2005).

- In recent decades, gestational age decreased in a linear fashion from 1964 to 2007 in a similar way for MZ and DZ twins. Changes in birth weight depended on gestational age. The decrease in gestational age and change in birth weight in twins are sources of concern, especially for very preterm twins, for whom birth weight decreased (Gielen et al., 2010).
- Under the assumption that the spontaneous DZ twinning rate is a sensor of fecundity, our population-based data after age-adjustment indicates a stable 'high' fecundity for the East Flanders population (Derom et al., 2011).
- Whereas birth weight discordancy within monozygotic twin pairs cannot be used as an indicator of chorionicity (Gielen et al., 2009), a monochorionic placenta remains an excellent predictor of monozygosity and monozygosity diagnosis based on the structure of the fetal membranes can be considered accurate in almost all instances. In a consecutive series of 2006 monochorionic pairs and 3156 opposite-sexed twins all but one of the monochorionic twins were of the same sex and all but one of the opposite-sexed twins were dichorionic (table 1).
- Placental telomere length decreases during the third trimester of gestation of live-born twins with approximately 25% and is influenced by parity, indicating that telomere shortening may play a role in senescence of the placenta (Gielen et al., 2014) .
- In twins, a risk group for low birth weight and fetal growth restriction, a significant proportion of fetal growth restriction could be attributed to *in utero* exposure to particulate air pollution. Air pollution is associated with small for gestational age and birth weight in moderate to late preterm born twins. The within-pair difference in birth weight increases with higher air pollution exposure during the last month of pregnancy (Bijnens et al., 2016).

Cognitive and behavioural development

- A significant effect of chorion type on the heritability of two IQ subtests was found: the MC twins resembled each other more than the DC-MZ twins on the subscales of Arithmetic and Vocabulary. The effect accounts for respectively 14% and 10% of the total variance (Jacobs et al., 2001). X-inactivation, however, is not likely involved as no significant interaction was found between sex and chorionicity (Peerbooms et al., 2010).

- Lower birth weight is a causal risk factor for child problem behaviour, the effects of which may well extend into adulthood (van Os et al., 2001; M. C. Wichers et al., 2001) .
- Twins with lower birth weight and cord knots had lower IQ scores. The aetiology of IQ is largely distinct from that of birth weight and cord knots, and non-shared environment may influence the observed relationships (Antoniou et al., 2013).

Cardiovascular and metabolic phenotypes

- An adverse prenatal environment during twin pregnancies has small, but permanent effects on health in adult life: adult body composition, blood pressure, glucose-metabolism and renal function have part of their origins in utero, but they are programmed through different prenatal environmental influences. Furthermore, the prenatal environment seems to program men and women in a different way (Gielen et al., 2005; Loos, et al., 2001b; Loos, et al., 2001c) . The satiety signal leptin, that regulates food intake and energy expenditure, may act as a growth-promoting signal during fetal development and the leptin receptor could have a possible role in explaining the inverse relationship between birth weight and the development of metabolic diseases in adulthood (Souren et al., 2008) .
- Growth during infancy is associated with birth weight and gestational age. From 0 to 1 month, environmental factors are most important for growth, whereas genetic factors become more important over time. This is a first step in identifying age windows for future counseling and interventions on the effects of accelerated growth (Touwslager et al., 2011).
- DNA methylation variability at growth-related imprints does not contribute to overweight in monozygotic twins discordant for BMI (Souren et al., 2011).
- Severe intra-uterine growth differences observed within monozygotic twins are not associated with long-lasting DNA methylation differences in cells composing saliva. Additionally, our results indicate that uneven cell type composition can lead to spurious results and should be addressed in epigenomic studies (Souren et al., 2013).
- Longitudinal evidence of telomere length tracking from birth to adulthood shows inverse associations of residential traffic exposure in association with telomere length at birth as well as accelerated telomere shortening in the first two decades of life (Bijnens, Zeegers, et al., 2017). Telomere length in placental tissue and in buccal cells in young adulthood and the geocoding of residential addresses both at birth and in young adulthood as well as residential traffic and greenness exposure was used to study this association.

- Residential greenness has persistent effects on blood pressure: lower residential greenness in the early-life environment was independently associated with a higher adult blood pressure (Bijnens, Nawrot, et al., 2017).

Stress and mental health

- Stress-induced increase in negative affect regulates the individual sensitivity to small daily stress, is associated with elevated cortisol levels, (sub)clinical depression and (sub)clinical psychotic symptoms and influenced by genes, which is indicative of gene-environment interaction. Neuroticism, as measured by Eysenck questionnaire, may index an environmental risk for decreased daily life positive affect levels and a genetic as well as an environmental risk for increased negative affect variability (Jacobs et al., 2011). The findings are also consistent with the hypothesis that adult daily life stress-sensitivity is the result of sensitization processes initiated by developmental stress exposures. Genes associated with depression may act by accelerating the process of stress-induced sensitization (Wichers et al., 2009).
- Currently more than 400 twin pairs, their siblings in the age range of 15-35 years are taking part in a project (TwinsCan) that aims to examine genetic and environmental underpinnings of behavioural and cognitive processes (e.g., aberrant salience attribution and disturbed neurocognition) and their relation with multidimensional psychopathology by using novel experimental tasks such as the white noise speech illusion task (Pries et al., 2017), the digital social peer evaluation experiment (Menne-Lothmann et al., 2017), and the experience sampling method (ESM) to assess the moment-to-moment dynamic changes of mental states. The TwinsCan projects aims to shed light on biological mechanisms underlying mental disorders by analysing a wide collection of biological material that include placenta samples, cortisol levels, and genome- and epigenome-wide molecular data (Pries et al, 2019). In this direction, recent ESM studies of the first wave of the TwinsCan cohort investigated the influence of childhood adversity and genetic liability on momentary mental states. The network analysis of the ESM data revealed that proxy genetic liability for psychopathology was associated with more densely connected network structure of the emotions, which include 'cheerful', 'insecure', 'relaxed', 'anxious', 'irritated', and 'down' items (Hasmi et al., 2017). A recent gene-environment interaction study using the ESM data has demonstrated

that polygenic risk score for schizophrenia interacts with childhood adversities to influence negative affect, positive affect, and subtle psychosis expression (Pries et al., Submitted for publication).

Discussion

Criticism has been addressed to the classical twin studies with regard to the assumption of equal intrauterine environments of MZ twins. The most important examples of potentially unequal intrauterine environments are undoubtedly chorionicity, zygosity and the origin of the pregnancy, spontaneous or ART. Other factors, however, must also be considered: gestational age, birth sequence, birth weight, insertion of the umbilical cord, the mode of delivery and presentation of both twins.

With a sizeable group of more than 1000 DC-MZ, 2000 MC-MZ and 3000 ART twin pairs the EFPTS can perform twin studies with less biases, i.e. studies that are based on the crucial assumption that MZ and DZ twins, spontaneous and ART twins, have a similar intrauterine environment. Previous results have indicated that this could not be the case (Delbaere et al., 2007; Verstraelen et al., 2005). Comparison of DC-MZ, MC-MZ and DZ twins will allow better evaluation of the degree of gene-environment interactions as the prenatal environment is concerned. In contrast to all DC-MZ and DZ twins, MC-MZ twins share their chorion, most of them share their blood supply and therefore, their immune system during intrauterine life. This could have long term effects on phenotypes in later life (Craig & Saffery, 2015).

There is further evidence that ART can induce epigenetic variation that might be transmitted to the next generation and that subfertility itself is a risk factor for imprinting diseases (Huntriss et al., 2018). With more than 3000 twin pairs and 200 triplet sets being born after various techniques of ART, whether born after fertility treatment without further intervention (ovulation induction only) or after IVF/ICSI or related techniques, EFPTS is the ideal resource for the long-term follow-up study of these multiples on a population-based manner.

After 55 years, EFPTS has still the capacity to continue to collect prospectively perinatal and biological data at birth, phenotypes in later life and link both of them. As retrospective analysis of the placentation is still impossible to carry out and multiples born after ovulation induction

only are hard to detect retrospectively, the effect of chorion type, origin of the pregnancy and the epigenetic phenomena on phenotypes in later life will remain one of the primary goal of the research with EFPTS. As such, EFPTS shows that twin research remains a reliable tool to study not only the genetic determination of different phenotypes. It provides an unparalleled opportunity to study links between the (epi)genome, the intra-uterine environment, air pollution exposure and (sub)clinical outcomes.

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