CHAPTER 5

INCREASED TIME TO PREGNANCY IS ASSOCIATED WITH SUBOPTIMAL NEUROLOGICAL CONDITION OF 2-YEAR-OLDS

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**ABSTRACT**

**Objective:** To evaluate whether time to pregnancy (TTP) is associated with neurological condition of 2-year-old children born to subfertile parents.

**Design:** Data collected in a prospective, assessor-blinded follow-up study were used for cross-sectional analyses.

**Patients:** Participants were the singletons of the Groningen ART cohort study: all children were born to subfertile couples (n = 209). The active waiting TTP of the couples was obtained from fertility charts was recorded in years and months, and was converted to decimal years.

**Main Outcome Measure:** The presence of minor neurological dysfunction (MND), assessed with the Hempel examination.

**Results:** MND was present in 16 (7.7%) children. TTP of children with MND (median 4.1, range 1.6-13.2) was significantly longer than that of children without MND (median 2.8, range 0.1-13.3; Mann-Whitney U-test p = 0.014). Logistic regression analysis on the contribution of TTP to MND resulted in a crude OR of 1.27 (95%CI: 1.06-1.54). After correction for gestational age, parental age and parental level of education, the association remained statistically significant: OR = 1.30 (95%CI: 1.05-1.61).

**Conclusion:** Increased TTP was associated with suboptimal neurological development in 2-year-old children. This suggests that subfertility and its determinants are involved in the genesis of neurodevelopmental problems.
**INTRODUCTION**

It is well established that children conceived with assisted reproductive techniques (ART), like *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI), are at increased risk for preterm birth and low birthweight (Helmerhorst *et al.* 2004), conditions associated with developmental problems. Previously, we reported that neurological condition at 2 years was not affected by IVF/ICSI, that is, it was not affected by ovarian hyperstimulation nor by the *in vitro* procedure (Schendelaar *et al.* 2011). An increasing body of evidence suggests that subfertility *per se*, rather than fertility treatment, is associated with adverse outcomes (Davies *et al.* 2012b, Draper *et al.* 1999).

In order to evaluate the effect of subfertility, time to pregnancy (TTP) may be used. The notion that TTP can be used as a proxy for the severity of subfertility is based on models that have shown that TTP is an important predictor of the chance of pregnancy in subfertile couples (van der Steeg *et al.* 2007, van Loendersloot *et al.* 2010). About 10-20% of couples are subfertile: they fail to achieve a successful pregnancy after 12 months or more of appropriate, timed, unprotected intercourse (Juul *et al.* 1999). Other studies demonstrated that increased time to pregnancy is associated with more Caesarean sections, pregnancy-induced hypertension, preterm birth, perinatal death, and birth defects (Basso and Baird 2003, Jaques *et al.* 2010, Raatikainen *et al.* 2010, Seggers *et al.* 2012, Thomson *et al.* 2005, Zhu *et al.* 2006). Zhu *et al.* demonstrated that increasing TTP is correlated with a modest delay in psychomotor development in 18-month-old children (Zhu *et al.* 2009). However, the association between prolonged TTP and detailed neurological outcome is not known. Therefore, the aim of this study is to evaluate the association between TTP and neurological status of 2-year-old children.

**METHODS**

This study is part of the Groningen ART cohort study, a prospective assessor-blinded longitudinal study that focuses on developmental outcome of children born following IVF and ICSI. Two hundred and nine singletons were included in the analyses: 66 children born after controlled ovarian hyperstimulation-IVF/ICSI, 56 born after modified natural cycle-IVF/ICSI and 87 children born naturally to subfertile couples. As group status did not affect neurological condition at 2 years (Schendelaar *et al.* 2011), we pooled the groups to form a set of 209 singletons born to subfertile couples.

Information on TTP was obtained from fertility charts and is recorded in years and months. Subsequently, TTP was converted into decimal years. TTP was defined as the time between the active child wish (i.e. the start of timed unprotected...
intercourse) of the couple and conception. Note that in case of miscarriage, TTP had a new onset and ended at conception of the child included in the present study. This explains why subfertile couples may have a TTP of < 1 year.

Around the time of the second birthday of children, neurological condition was assessed using the neurological examination according to Hempel (Hempel 1993b). In the Hempel assessment five domains of function are assessed as typical or deviant: fine motor function, gross motor function, posture and muscle tone, reflexes, and visuomotor function. Children were classified as neurologically normal, simple minor neurological dysfunction (MND) or complex MND (Hadders-Algra 2002). Children are classified as neurologically normal if no domains are deviant or only the domain of reflexes. Simple MND implies the presence of one deviant domain (except reflexes) and it indicates a suboptimal, yet normal form of brain function. Complex MND implies the presence of multiple deviant domains and it represents the clinically relevant form of MND.

Details on the inclusion period and materials and methods have been reported previously (Middelburg et al. 2010, Schendelaar et al. 2011). Parents gave written informed consent for participation of their child in the study. The study design was approved by the ethics committee of the University Medical Center Groningen.

**Statistical analysis**

First, we reported background characteristics of the Groningen ART cohort in a descriptive table. Second, the Mann-Whitney U-test was performed to evaluate differences in TTP between children with or without MND. Third, multiple logistic regression analyses were used to study the effect of TTP on the occurrence of MND (either simple or complex MND) while correcting for gestational age in weeks, parental age in years and parental level of education (high or not, used as an indicator of socio-economic status). Fourth, we repeated the multiple logistic regression analysis to evaluate the effect of TTP on complex MND alone, i.e. on the clinically relevant form of MND. We used Predictive Analytics SoftWare (PASW) version 18.0 to analyse the data. Probability values of < 0.05 were considered statistically significant.

**Results**

Table 1 shows the background characteristics of the children assessed (n = 209). MND was present in 16 (7.7%) children: simple MND occurred in 10 children and complex MND in 6 children. TTP pregnancy showed a skewed distribution, median (range): 3.0 (0.1-13.3) years. TTP of children with MND (median 4.1, range 1.6-13.2) was significantly longer than that of children without MND (median 2.8, range
0.1-13.3; Mann-Whitney $U$-test $p = 0.014$, see Figure 1). Logistic regression of the contribution of TTP in years to the presence of MND (either simple or complex MND) resulted in a crude odds ratio (OR) of 1.27 (95% confidence interval (CI): 1.06-1.54; $p = 0.012$). After correction for gestational age, parental age and parental level of education, the association remained statistically significant: adjusted OR = 1.30 (95%CI: 1.05-1.61; $p = 0.018$). Logistic regression of the contribution of TTP in years to complex MND resulted in similar associations: crude OR = 1.38 (95%CI: 1.07-1.77; $p = 0.014$), adjusted OR = 2.29 (95%CI: 1.03-5.09; $p = 0.041$).

The association between TTP and MND was mainly brought about by deviations in the domain posture and muscle tone ($n = 7$): crude OR = 1.36 (95%CI: 1.07-1.74; $p = 0.012$). After correction for gestational age, parental age and parental level of education, this association lost statistical significance: adjusted OR = 1.31 (95%CI: 0.97-1.79; $p = 0.081$). The other domains did not show a statistically significant association with TTP.

Figure 1. TTP in neurologically normal children and in children with minor neurological dysfunction. Horizontal bars indicate median values, boxes interquartile ranges, vertical lines full ranges and small circles extreme values.
Part 3 — The Groningen ART Cohort Study

Table 1. Infant, gestational, birth and parental characteristics of the singletons participating in the Groningen ART cohort study.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 209</th>
</tr>
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<tbody>
<tr>
<td>Male gender, n (%)</td>
<td>108 (52)</td>
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<tr>
<td>Firstborn, n (%)</td>
<td>136 (65.1)</td>
</tr>
<tr>
<td><strong>Gestational characteristics</strong></td>
<td></td>
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<tr>
<td>Smoking during pregnancy, n (%)</td>
<td>23 (11)</td>
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<tr>
<td>Use of folic acid during pregnancy*, n (%)</td>
<td>191 (91.4)</td>
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<tr>
<td>Pregnancy-induced hypertension, n (%)</td>
<td>25 (12)</td>
</tr>
<tr>
<td>Gestational diabetes, n (%)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td><strong>Birth characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks), median (range)</td>
<td>39.6 (1.9)</td>
</tr>
<tr>
<td>Preterm birth (&lt;37 weeks), n (%)</td>
<td>20 (9.6)</td>
</tr>
<tr>
<td>Birthweight (g), mean (SD)</td>
<td>3460 (575)</td>
</tr>
<tr>
<td><strong>Parental characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Time to pregnancy in years*, median (range)</td>
<td>3.0 (0.1-13.3)</td>
</tr>
<tr>
<td>Maternal age at conception, median (range)</td>
<td>33.0 (22.2-40.9)</td>
</tr>
<tr>
<td>Paternal age at conception*, median (range)</td>
<td>35.1 (25.5-56.1)</td>
</tr>
<tr>
<td>Education level mother high*, n (%)</td>
<td>83 (39.7)</td>
</tr>
<tr>
<td>Education level father high*, n (%)</td>
<td>79 (37.8)</td>
</tr>
</tbody>
</table>

Note that in case of miscarriage, time to pregnancy had a new onset and ended at conception of the child included in the present study. This explains why subfertile couples may have a time to pregnancy of < 1 year.

Values are number (percentage), or mean (standard deviation), or median (range).

*Missing values: education level father n = 4, use of folic acid n = 3, paternal age at conception n = 4, time to pregnancy n = 1.

*bUniversity education or vocational colleges.

**Discussion**

TTP was positively associated with MND, including the clinically relevant form complex MND. This finding is in line with the study of Zhu et al., who demonstrated that increasing TTP is correlated with a modest delay in psychomotor development in 18-month-old children (Zhu et al. 2009). A major strength of the present study is the application of sensitive and age-specific methods to assess neurological condition. In addition, attrition was minimal (3%), and selection bias was reduced as couples were
recruited prospectively during the third trimester of pregnancy. Note that we were able to pool the three original study groups to form one subfertile group as group status did not affect neurological outcome. In this way, we could increase the power of the study to detect an association between TTP and MND. We checked whether additional correction for group status in the multiple analyses altered the results; it did not (data not shown). A limitation of the study is that twins were not included. This means that the results cannot be generalized to children born after multiple gestation. Furthermore, it should be noted that only six children had complex MND, which means that caution is deserved in the interpretation of the association between TTP and complex MND. In conclusion, the present data suggest that increased TTP is associated with suboptimal neurological development. This implies that factors associated with subfertility may play a role in the genesis of neurodevelopmental problems. Further exploration of the associations between subfertility and health outcome in offspring is necessary for the correct counselling of subfertile couples.

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