Paternal age over 40 years is associated with increased trisomy 21 risk independently of maternal age: a retrospective cohort study

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INTRODUCTION

- Trisomy 21 is the most common chromosomal abnormality in humans (1) and is the cause of 95% of Down syndrome cases.
- The impact of maternal age on trisomy 21 risk is well established, however there is disagreement in the literature concerning the impact of paternal age on trisomy 21 risk:
  - Using data from the New York State Department of Health Congenital Malformations registry, Hisch et al. (2) found increased paternal age to be associated with increased Down syndrome risk.
  - Using data from the United Stations Natality database, Thompson (3) found that increased paternal age was not associated with increased Down syndrome risk.
- Previous literature has focused on the number of Down syndrome cases at birth, however, prenatal screening and diagnostic tests allow for the detection of trisomy 21 and Down syndrome before birth.

OBJECTIVE

The objective of our study was to explore the association between paternal age and prenatal trisomy 21 risk.

METHODS

Between January 2014 and August 2018, pregnant women who underwent trisomy 21 screening at the Ovo Clinic in Montreal, Quebec, Canada completed an optional questionnaire concerning paternal age and socio-demographic information. Trisomy 18 screening was completed concurrently.

Trisomy 21 screening was a two-step procedure:

1. Biochemical analysis (PAPP-A, FβHCG, AFP and PIGF) of maternal serum and nuchal transparency results from prenatal ultrasonography were combined to provide a risk assessment as follows:
   Low: < 1/2500
   Moderate: 1/100 to 1/2500
   High: > 1/100
2. Any patient with moderate or high risk in the first step (for either trisomy 21 or 18) underwent cell free DNA based non-invasive prenatal testing, which provides a risk assessment of either low or high trisomy 21 risk.

Diagnosis of trisomy 21 is confirmed via amniocentesis or chorionic villus sampling.

Statistical Analysis

Three multivariate binomial regression models assessed the association between paternal age (≥ 40 years) and trisomy 21 risk, defined as follows:

1. Moderate or high risk for trisomy 21 based on biochemical/ultrasound screening;
2. High trisomy 21 risk on foetal DNA screening among all patients who underwent foetal DNA screening;
3. High trisomy 21 risk on foetal DNA screening among patients who had moderate or high risk based on biochemical/ultrasound screening.

All three models were controlled for maternal age (≥ 35 years) and maternal ethnicity (self-reported).

RESULTS

The study sample comprised of 7468 pregnant women who underwent biochemical/ultrasound trisomy 21 screening and completed the questionnaire.

Table 1. Prenatal biochemical and ultrasound trisomy 21 screening results.

Variable	Entire sample	Males aged <40 years	Males aged ≥40 years	p-value[a]
n (%)	7468 (100%)	6618 (88.6%)	850 (11.4%)	
Risk categories				
Low risk, n (%)	6675 (89.4%)	5979 (90.3%)	696 (81.9%)	< 0.001
Mod. or high risk, n (%)	793 (10.6%)	639 (9.7%)	154 (18.1%)	
Biochemical and ultrasound characteristics (units: multiples of median)				
PAPP-A, mean (sd)	1.06 (1.56)	1.04 (0.74)	1.22 (4.13)	0.21
FβHCG, mean (sd)	1.18 (0.80)	1.18 (0.80)	1.18 (0.80)	0.96
AFP, 1st, mean (sd)	1.13 (0.62)	1.13 (0.62)	1.14 (0.63)	0.47
AFP, 2nd, mean (sd)	1.06 (0.35)	1.09 (0.38)	0.95 (0.17)	0.19
PIGF	1.03 (0.44)	1.02 (0.44)	1.06 (0.48)	0.01
Nuchal transparency, mean (sd)	1.02 (0.21)	1.02 (0.20)	1.04 (0.28)	0.02

[a] : p-values for differences between male age groups; Optimo risk categories: Chi-Square test, biochemical and ultrasound characteristics: two-sample t-tests.
PAPP-A: pregnancy-associated plasma protein A.
FβHCG: serum free β human chorionic gonadotropin.
AFP: alpha fetoprotein, sampled twice during the screening process.
PIGF: placental insulin-like growth factor.

Table 2. Association of paternal age with biochemical and ultrasound trisomy 21 screening results.

Variable	OR[a] (95% CI)	p-value[b]
Univariate model		
Paternal age ≥ 40 years	2.07 (1.71-2.51)	< 0.001
Multivariate model[c]		
Paternal age ≥ 40 years	1.25 (1.02-1.55)	0.04
Maternal age ≥ 35 years	2.77 (2.35-3.26)	< 0.001

[a]Odds ratios of a moderate or high-risk result on biochemical and ultrasound trisomy 21 screening test.
[b]p-values calculated as probability > |t|.
[c] multivariate model adjusted for maternal ethnicity (self-reported).

Adjusted ORs for trisomy 21 risk based on foetal DNA screening (among all patients who underwent foetal DNA screening and among those with moderate or high biochemical/ultrasound risk) were not statistically significant at α = 0.05.

CONCLUSIONS

- Independent of maternal age and ethnicity, paternal age ≥ 40 years is associated with increased odds of moderate or high trisomy 21 risk on biochemical/ultrasound screening:
  - aOR: 1.25 (95% CI: 1.02-1.54, p = 0.04).
- There are significant differences in PIGF levels and nuchal transparency between patients with male partners aged < 40 or ≥ 40 years (p = 0.01 and p = 0.02, respectively) which may explain the observed association between trisomy 21 risk on biochemical/ultrasound screening and paternal age.
- No statistically significant association between paternal age ≥ 40 years and foetal DNA trisomy 21 screening risk was found which may be due to a lack of statistical power.
- The potential clinical applications of these findings warrant further study.

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