Prenatal identification of trisomy 18 (Edwards syndrome)

Thesis submitted for the degree of PhD

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I confirm that the work presented in this thesis is my own.

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Abstract

This thesis is a critical literature review of trisomy 18 (Edwards syndrome), focused on maternal serum and ultrasound markers between 10 and 20 weeks' gestation. Based on comprehensive meta-analyses, existing findings are clarified, new knowledge has emerged, and novel statistical modeling demonstrates clinically useful algorithms to guide screening policies.

Trisomy 18 is, after Down syndrome, the autosomal aneuploidy with the highest birth prevalence, about 2.4/10,000. Only 1 in 5 live born survives to two weeks, with 1 in 20 surviving one year. Strategies for identifying trisomy 18 in early pregnancy rely on re-interpretation of markers measured as part of Down syndrome screening. Diagnosis requires collecting fetal or placental material obtained from an invasive procedure (amniocentesis or a chorionic villus sampling) and subsequent karyotyping or specific aneuploidy testing such as fluorescent in situ hybridization.

The second trimester Triple Test (serum markers alpha-fetoprotein, unconjugated estriol and human chorionic gonadotropin [hCG]) has an 81% detection rate at a 0.4% false positive rate. Adding pregnancy-associated plasma protein-A (PAPP-A) is effective; the detection rate improves to 88% while false positives are reduced to 0.1%. In the first trimester Combined Test, the serum markers (free β hCG and PAPP) in combination with unbiased estimates of ultrasound marker nuchal translucency (NT) thickness, yields detection and false positive rates of 86% and 0.2%, respectively. For these tests, hCG and free β hCG measurements are essentially interchangeable. Combining existing markers from both trimesters into a Full Integrated Test (NT, PAPP-A, and the Triple Test), also yields high performance (91% detection rate at 0.2% false positive rate). Ultrasound markers, apart from NT, are not suitable for routine practice, but some could be used in specialist centers. In the future, testing of circulating cell free nucleic acids in maternal plasma may allow for a reduction in the use of invasive procedures.

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Abbreviations

AFP	=	alpha-fetoprotein
ASD	=	atrial septal defects
CPC	=	choroid plexus cysts
CVS	=	chorionic villus sampling
DNA	=	deoxyribonucleic acid
DR	=	detection rate (equivalent to sensitivity)
FISH	=	fluorescent in situ hybridization
FPR	=	false positive rate (equivalent to 1-specificity)
free β	=	the free beta subunit of hCG (hCG is composed of alpha and beta subunits)
hCG	=	human chorionic gonadotropin
log	=	base 10 logarithm
LR	=	likelihood ratio
MoM	=	multiple of the median
NB	=	nasal bone
NT	=	nuchal translucency
OAPR	=	odds of being affected given a positive result
ONTD	=	open neural tube defect
PAPP-A	=	pregnancy associated plasma protein A
PIV	=	pulsatility index for veins (in relation to ductus venosus)
PPV	=	positive predictive value (%)
qfPCR	=	quantitative polymerase chain reaction
RNA	=	ribonucleic acid
RR	=	relative risk
SD	=	standard deviation
SNP	=	single nucleotide repeat
STR	=	short tandem repeats
uE3	=	unconjugated estriol
VSD	=	ventricular septal defects