PRENATAL DIAGNOSIS INFORMATION SOURCES

- TROPHOBLAST / PLACENTA
  - CARYOTYPE, ADN, BIOCHEMISTRY
- AMNIOTIC FLUID
  - CELLS: CARYOTYPE, ADN, BIOCHEMISTRY
  - FLUID: BIOCHEMISTRY
- FETAL BLOOD
  - CARYOTYPE, ADN, SEROLOGY, HEMATOLOGY, BIOCHEMISTRY
- FETUS
  - TISSUES (BLOOD, SKIN, MUSCLE, LIVER)
  - "PHENOTYPE"
  - "WELL-BEING"
  - "BEHAVIOUR"
- MATERNAL BLOOD
  - FETAL CELLS, FETAL DNA

PRENATAL DIAGNOSIS
INTRODUCTION

30 years ago, fetal medicine did not exist; the fetus, concealed in the uterus, was a passenger, not a patient.

During the last three decades, owing to the development of cardiotocography, ultrasound and Doppler imaging, sampling techniques, biochemistry, genetics and molecular biology, a considerable body of knowledge has been accumulated, allowing a more precise definition of fetal physiology, anomalies and diseases.

The fetus has thus become a patient, that we can diagnose, follow and treat.

The aim of this lecture is to present an overview of the various methods available today for the diagnosis of fetal anomalies and/or diseases.

By its nature, fetal medicine requires the synergistic use of various techniques and expertises and is a good example of a multidisciplinary team work.

PRENATAL DIAGNOSIS
WHICH TEST TO USE ?

- **QUESTION TO BE ANSWERED :**
  CHOICE OF THE APPROPRIATE INFORMATION SOURCE
- **GESTATIONAL AGE :**
  CHOICE OF THE APPROPRIATE METHOD
- **RISK OF THE VARIOUS SAMPLING METHODS**

PRENATAL DIAGNOSIS
CHOICE OF THE SAMPLING METHOD

GESTATIONAL AGE

- ≤ 13 WKS : CVS
- ≥ 15 WKS : AMNIOCENTESIS
- ≥ 20 WKS : AMNIOCENTESIS
  FBS

PRENATAL DIAGNOSIS SAMPLING METHODS

AMNIOCENTESIS

FETAL BLOOD SAMPLING (FBS)

CHORIONIC VILLUS SAMPLING (CVS)

FETAL TISSUES BIOPSIES (SKIN, MUSCLE, LIVER)

PRENATAL DIAGNOSIS
AMNIOCENTESIS

INDICATIONS

DETERMINATION OF FETAL CARYOTYPE

NEURAL TUBE DEFECTS

MENDELIAN DISEASES

PRENATAL DIAGNOSIS
AMNIOCENTESIS

DETERMINATION OF FETAL CARYOTYPE:

- ADVANCED MATERNAL AGE (≥35 YRS)
- HIGH RISK OF ANEUPLOIDY ON SCREENING
- HISTORY OF CHROMOSOMAL ANOMALY
- PARENTS CARRIERS OF A BALANCED TRANSLOCATION
- X-LINKED DISEASES
- ULTRASOUND-DETECTED FETAL ANOMALIES
- MATERNAL ANXIETY

PRENATAL DIAGNOSIS
AMNIOCENTESIS

NEURAL TUBE DEFECTS

MEASUREMENT OF AMNIOTIC ALPHA-FETOPROTEIN AND ACETYL-CHOLINESTERASE CONCENTRATIONS:

ELEVATION OF MATERNAL SERUM aFP

HISTORY OF NTD

PRENATAL DIAGNOSIS
AMNIOCENTESIS

MENDELIAN DISEASES

MEASUREMENT OF ENZYME ACTIVITIES OR METABOLITES CONCENTRATIONS IN AMNIOTIC FLUID OR AMNIOCYTES

ANALYSES OF FETAL DNA FROM AMNIOCYTES

PRENATAL DIAGNOSIS
AMNIOCENTESIS

TECHNIQUES

BLIND SAMPLING

ULTRASOUND-DIRECTED PUNCTURE

SAMPLING UNDER ULTRASOUND GUIDANCE

PRENATAL DIAGNOSIS
AMNIOCENTESIS

CONTRIBUTIONS OF ULTRASOUND

CONFIRMATION OF FETAL LIFE
CONFIRMATION OF GESTATIONAL AGE
DIAGNOSIS OF MULTIPLE GESTATIONS
DIAGNOSIS OF FETAL ANOMALIES

SELECTION OF THE OPTIMAL SAMPLING SITE
REDUCTION OF UNSUCCESSFUL SAMPLINGS
REDUCTION OF BLOODY SAMPLES
REDUCTION OF FETAL LESIONS

PRENATAL DIAGNOSIS
AMNIOCENTESIS

COMPLICATIONS

CHORIOAMNIONITIS	< 1/1000
FETAL LESIONS	-
AMNIOTIC FLUID LEAKAGE	≤ 1/100
FETAL DEATH, MISCARRIAGE	0,5 - 1/100
RH SENSITIZATION	~ 5 %

PRENATAL DIAGNOSIS
FETAL BLOOD SAMPLING

INDICATIONS

DETERMINATION OF FETAL CARYOTYPE
MATERNAL INFECTIONS
MATERNAL ALLO-IMMUNISATION
FETAL BIOLOGY
INTRA-UTERINE TREATMENT
(FETAL DNA ANALYSIS)

PRENATAL DIAGNOSIS
FETAL BLOOD SAMPLING

TECHNIQUES

POSSIBLE FROM 18 WKS

US-GUIDED PUNCTURE OF:

1. **UMBILICAL VEIN IN THE CORD**
   - PLACENTAL INSERTION
   - UMBILICAL INSERTION
   - FREE LOOP
2. **INTRA-HEPATIC PORTION OF THE UMBILICAL VEIN**
3. **CARDIAC CHAMBERS**

PRENATAL DIAGNOSIS
FETAL BLOOD SAMPLING

COMPLICATIONS

RUPTURE OF MEMBRANES

HEMORRHAGE AT PUNCTURE SITE

FETAL BRADYCARDIA (TRANSITORY)

FETAL DEATH (≤ 1%)

PRENATAL DIAGNOSIS
CHORIONIC VILLUS SAMPLING (CVS)

POTENTIAL ADVANTAGES:

EARLY DIAGNOSIS

DETERMINATION OF FETAL CARYOTYPE:
- DIRECT PREPARATIONS
- CELL CULTURES

DIRECT MEASUREMENT OF ENZYMATIC ACTIVITIES

SOURCE OF FETAL DNA

PRENATAL DIAGNOSIS
CHORIONIC VILLUS SAMPLING (CVS)

TECHNIQUES

TRANSCERVICAL SAMPLING

US-GUIDED ASPIRATION OR BIOPSY

TRANSABDOMINAL SAMPLING

US-GUIDED ASPIRATION OR BIOPSY

(TRANSVAGINAL SAMPLING)

CVS VERSUS AMNIOCENTESIS
META-ANALYSIS (COCHRANE DATABASE)

	CVS	AMNIOCENTESIS
SAB (≤28 WKS):	259/3646 (7,1%)	133/2634 (5.05%)
	OR 1.53 (1.16 - 2.01)	
TOTAL PREGNANCY LOSS:	395/3646 (10,83%)	211/2634 (8,01%)
	OR 1.49 (1.19 - 1.56)	

PRENATAL DIAGNOSIS
CVS VERSUS MA

1. TOTAL PREGNANCY LOSS AFTER CVS IS HIGHER THAN AFTER MA
2. CVS IS ASSOCIATED WITH A GREATER NUMBER OF INADEQUATE SAMPLES, CULTURE FAILURES AND AMBIGUOUS RESULTS
3. CVS SHOULD NOT BE PERFORMED BEFORE 10 WKS, CONSIDERING THE RISK OF LRD'S PROBABLY ASSOCIATED WITH EARLIER SAMPLINGS

PRENATAL DIAGNOSIS
EARLY AMNIOCENTESIS

DEFINITION :

- MID-TRIMESTER AMNIOCENTESIS (MA) : ≥ 15 WKS
- EARLY AMNIOCENTESIS (EA) : < 15 WKS

AREA OF CONCERN :

- SAFETY
- CYTOGENETIC RELIABILITY

PRENATAL DIAGNOSIS
EA VERSUS TA-CVS

KING'S COLLEGE TRIAL:

EARLY AMNIOCENTESIS (10-13 WKS): 238

TA-CVS (10-13 WKS): 250

EXCESS OF PREGNANCY LOSS: 4,7% (1,4-8,0)
IN THE EA GROUP

LANCET 1994; 344: 435-9

PRENATAL DIAGNOSIS
EA VERSUS TA-CVS

DANISH TRIAL:

EARLY AMNIOCENTESIS (11-13 WKS): 581

TA-CVS (10-12 WKS): 579

PREGNANCY LOSS:	5,4%	VERSUS 4,8%	p = 0,66
CLUB FOOT:	1,7%	VERSUS 0%	p < 0,01

LANCET 1997; 350: 697-703

PRENATAL DIAGNOSIS
EA VERSUS MA

RANDOMISED TRIAL (CEMAT)

	EA (11^{+0} - 12^{+6})	MA (15^{+0} -16^{+6})	p
N	2183	2185	
PREGNANCY LOSS:	7,6%	5,6%	0,012
AF LEAKAGE (<22 SEM.):	3,5%	1,7%	0,0007
CLUB FOOT:	1,3%	0,1%	0,0001
CYTOGENETIC FAILURE:	1,7%	0,2%	0,001

LANCET 1998; 351: 242-7

PRENATAL DIAGNOSIS

A. WHEN RISK FACTORS ARE ABSENT (SCREENING):

1. **FIRST-TRIMESTER MATERNAL SERUM SCREENING + NT:**
   - **PAPP-A / FREE beta-hCG:**
   - **NT**

   EVALUATION OF THE RISK OF FETAL ANEUPLOIDY (T21)
2. **SECOND-TRIMESTER MATERNAL SERUM SCREENING:**
   - **aFP: NTD (OTHER FETAL ANOMALIES)**
   - **aFP, hCG / free beta-hCG, UE3:**

   EVALUATION OF THE RISK OF FETAL ANEUPLOIDY (T21)
3. **ULTRASOUND**

PRENATAL SCREENING OF FETAL ANEUPLOIDY

CRITERIA USED	DETECTION RATE	AMNIOCENTESIS RATE
MATERNAL AGE :	30%	12-15%
MATERNAL AGE + aFP :	40%	10%
MAT. AGE + 2nd TRIM. BIOCHEM. :	>60%	5-8%
MAT. AGE+1st TRIM. BIOCHEM.+NT:	>80%	5%

RISK FACTORS FOR CONGENITAL ANOMALIES

- FAMILIAL HISTORY OF CONGENITAL ANOMALIES
- MOTHER AFFECTED BY A CONGENITAL ANOMALY
- PRIOR CHILD WITH A CONGENITAL ANOMALY
- BOTH PARENTS CARRIERS OF AN AUTOSOMAL RECESSIVE ANOMALY
- ETHNIC ORIGIN
- CONSANGUINITY
- PARENTS CARRIERS OF A BALANCED TRANSLOCATION
- MATERNAL DISEASE (EPILEPSY, DIABETES)
- EXPOSITION TO DRUGS (LITHIUM, RETINOIDS, DPH, TRIMETHADIONE, VALPROATE, COUMARINS)
- EXPOSITION TO TOXIC SUBSTANCES (ALCOHOL)
- INFECTIOUS AGENTS (RUBELLA, TOXOPLASMOSIS, CMV)
- ADVANCED MATERNAL AGE ($\geq$35 YRS)
- MULTIPLE GESTATIONS
- ELEVATION OR REDUCTION OF MATERNAL SERUM aFP CONCENTRATIONS
- 1ST OR 2ND-TRIMESTER SCREENING INDICATING A HIGH RISH OF FETAL ANEUPLOIDY

PRENATAL DIAGNOSIS

B. WHEN RISK FACTORS ARE PRESENT:

1. GENETIC COUNSELING

2. SAMPLING:
   CHORIOCENTESIS, AMNIOCENTESIS,
   FETAL BLOOD SAMPLING

3. ULTRASOUND (EMBRYOSCOPY)

INFORMATION BEFORE PRENATAL DIAGNOSIS (1)

1. FETAL DISORDER

- SEVERITY (AVERAGE AND EXTREMES)
- LONG-TERM CONSEQUENCES FOR CHILD, FAMILY AND COMMUNITY
- POSSIBILITIES OF TREATMENT AND THEIR EFFECTIVENESS

2. RISKS

- OCCURRENCE/RECURRENCE OF THE DISORDER
- RISKS OF THE DIAGNOSTIC PROCEDURE FOR MOTHER AND FETUS
- CHANCES OF MISDIAGNOSIS

INFORMATION BEFORE PRENATAL DIAGNOSIS (2)

3. PROCEDURES

- WHAT THEY INVOLVE
- TIME INTERVAL BEFORE A DIAGNOSIS CAN BE MADE
- WHAT PREGNANCY TERMINATION INVOLVES

4. OPTIONS

- IGNORE A LOW RISK OF ABNORMALITY
- PROCEED WITH PRENATAL DIAGNOSIS
- SEEK OTHER OPTIONS
  - HAI
  - ADOPTION
  - AVOID FURTHER REPRODUCTION

FETAL MEDICINE
MANAGEMENT OPTIONS

1. SEVERE ANOMALY / INCOMPATIBLE WITH SURVIVAL:
   TERMINATION OF PREGNANCY IS AN OPTION

2. CURABLE ANOMALY:
   OPTIMIZATION OF PERINATAL MANAGEMENT

3. INTRA-UTERINE TREATMENT

4. PARENTAL REASSURANCE WHEN ANOMALIES CAN BE EXCLUDED

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