Department of Obstetrics
&
Gynaecology

Prenatal & Preimplantation
Genetic Diagnosis
Fetal Therapy

Ospedale Regionale Microcitemie

WHO
Collaborating Centre for Community Control
of
Hereditary Diseases

TUTORING INVASIVE PRENATAL PROCEDURES

Giovanni Monni

Ho Chi Minh City, March, 2011

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PRENATAL INVASIVE PROCEDURES

CVS	AMNIOCENTESIS	CORDOCENTESIS
(>10 weeks)	(>15 weeks)	(>18 weeks)

UNDER CONTINUOUS ULTRASOUND GUIDANCE

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CHANGES IN THE APPROACH FOR INVASIVE PRENATAL DIAGNOSIS IN 35,127 CASES AT A SINGLE CENTER FROM 1977 TO 2004

Table 1. Invasive prenatal diagnosis for β-thalassemia

	PC	FS	CoC	CaC	AC	TC-CVS	TA-CVS	Total	PGD
1977–1981	949 (100%)	0	0	0	0	0	0	949	0
1982–1985	32 (3.2%)	67 (6.7%)	120 (12.0%)	6 (0.6%)	203 (20.3%)	572 (57.2%)	0	1,000	0
1986–1993	0	0	0	0	0	0	2,011 (100%)	2,011	0
1994–1999	0	0	0	0	0	0	1,477 (100%)	1,477	0
2000–2004	0	0	0	0	0	0	1,110 (100%)	1,110	42
Total	981	67	120	6	203	572	4,598	6,547	42

PC = Placentacentesis; FS = fetoscopy; CoC = cordocentesis; CaC = cardiocentesis; AC = amniocentesis; TA-CVS = transabdominal chorionic villi sampling; TC-CVS = transcervical chorionic villi sampling; PGD = preimplantation genetic diagnosis.

Table 2. Invasive prenatal diagnosis for karyotype analysis

	AC	TA-CVS	TC-CVS	CoC	HVS	Total
1977–1981	404 (100%)	0	0	0	0	404
1982–1985	894 (63.49%)	0	142 (10.09%)	372 (26.42%)	0	1,408
1986–1993	5,125 (63.30%)	2,438 (30.11%)	0	516 (6.37%)	18 (0.22%)	8,097
1994–1999	5,662 (60.96%)	3,228 (34.75%)	0	387 (4.17%)	11 (0.12%)	9,288
2000–2004	5,780 (61.88%)	3,346 (35.82%)	0	213 (2.28%)	2 (0.02%)	9,341
Total	17,865	9,012	142	1,488	31	28,538

AC = Amniocentesis; TA-CVS = transabdominal chorionic villi sampling; TC-CVS = transcervical chorionic villi sampling; CoC = cordocentesis; HVS = hepatic vein sampling.

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Monni, Fetal Diagn Ther 2006

CURRENT DISTRIBUTION (%) OF PRENATAL GENETIC TESTS IN CAGLIARI

CONDITIONS	CVS	AMNIO	PUBS
Maternal age (≥ 35 yrs)	40	55	5
Mendelian disorders	100	-	-
Karyotype for multiple anomalies	10	30	60
Congenital infections	10	60	30
1st Trim.US NT-NB + Biochem. screen	100	-	-
2nd Trim. Biochem. screen	5	90	5

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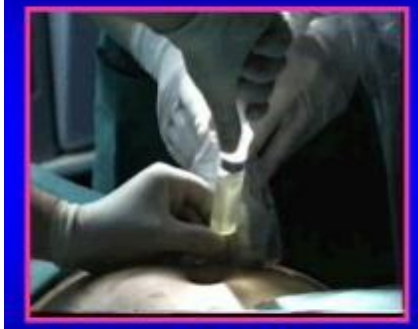
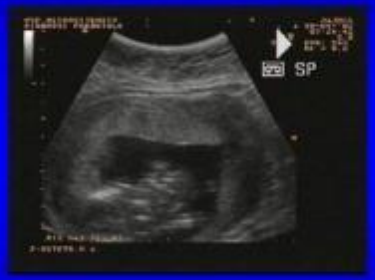
AMNIOCENTESIS IS A TECHNIQUE MUCH MORE STANDARDISED....





- The needle is 21 or 22 gauge
- The syringe (2 ml before and 15ml after)
- The amount of fluid for karyotype analysis
- No antibiotic prophylaxis

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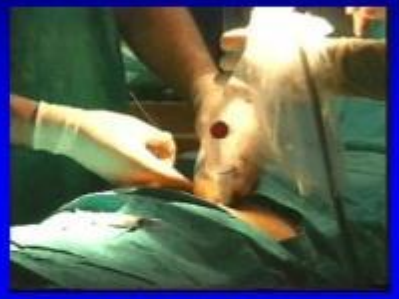
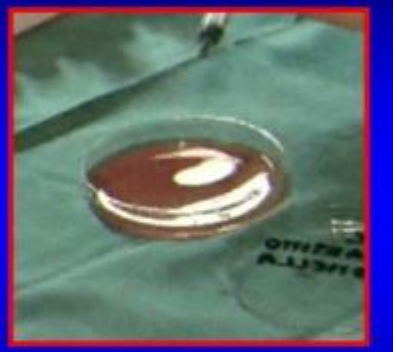
1ST TRIMESTER PLACENTAL BIOPSY (CHORIONIC VILLI SAMPLING) CVS





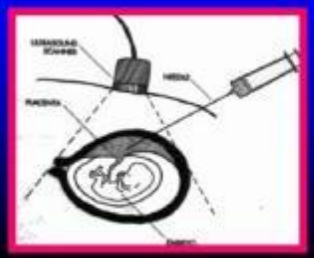
- Transabdominal or transcervical
- Catheter or syringe
- 18 or 20 gauge needle
- 2 ml or 20 ml syringe
- Manual or vacuum aspiration

There is little consensus regarding optimal technique

NUCHAL TRANSLUCENCY TEST IN WOMEN AGED 35 AND OLDER

- Could Decrease the Demand for Invasive Prenatal Diagnosis
- Could Lead to an Earlier Invasive Diagnosis of Aneuploidy by CVS

Zoppi, Obstet Gynecol 2001



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DECREASED USE OF CORDOCENTESIS

Middle cerebral artery Doppler is used to diagnose fetal anemia
Differentiation of alloimmune thrombocytopenia from maternal thrombocytopenia has decreased the need for fetal blood sampling
Specific DNA analysis are used for Mendelian disorders diagnosis
Fluorescence *in situ* hybridization is used for rapid aneuploidy (13, 18, 21, X, and Y)

The limited number of cordocentesis performed may lead to inadequate opportunities for Maternal Fetal Medicine fellows in training at many centers to confidently perform the procedure on their own.

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ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician-Gynecologists
Number 88, December 2007

Invasive Prenatal Testing for Aneuploidy

The following recommendation and conclusions are based primarily on consensus and expert opinion (Level C):

- Invasive diagnostic testing for aneuploidy should be available to all women, regardless of maternal age.
- Patients with an increased risk of fetal aneuploidy include women with a previous fetus or child with an autosomal trisomy or sex chromosome abnormality, one major or at least two minor fetal structural defects identified by ultrasonography, either parent with a chromosomal translocation or chromosomal inversion, or parental aneuploidy.
- Nondirective counseling before prenatal diagnostic testing does not require a patient to commit to pregnancy termination if the result is abnormal.

Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

Green-top Guideline No. 8

June 2010

Amniocentesis and Chorionic Villus Sampling

Amniocentesis and Chorionic Villus Sampling

This is the fourth edition of this guideline, which was previously published in October 1996, February 2000 and January 2005.

1. Aim

It is estimated that around 5% of the pregnant population (approximately 30 000 women per annum in the UK) are offered a choice of invasive prenatal diagnostic tests (most commonly amniocentesis or chorionic villus sampling). The type of diagnostic test available and offered is likely to vary depending upon the timing of any initial screening test that is performed. The aim of this guideline is to set a series of evidence-based standards to ensure a high level and consistency of practice in the provision and performance of amniocentesis and chorionic villus sampling.

FETAL LOSSES FOLLOWING TA-CVS

- Operator's experience
- Instruments
- Maternal age
- Gestational age
- Attempts
- Amount
- Associated pelvic pathology
- Bleeding
- Multiple gestation

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WORLD HEALTH ORGANISATION (WHO) RECOMMENDATIONS AND CRITERIA FOR CVS

- CVS only in Centers with a high level of expertise
- Centralisation of procedures
- Counselling
- CVS not performed before 10 wks
- Little damage to the placenta as possible
- Detailed U.S. at 18-20 wks
- Importance of strict follow up of delivery and neonatal data

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ENDPOINTS FOR THE ASSESSMENT OF TRAINING in PRENATAL INVASIVE PROCEDURES

- Fetal losses…..
- Need for several needle insertions…..
- Failure of the procedure…..
- Velocity of the procedure…..
- Patient's acceptance of the procedure…

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Amniocentesis and Chorionic Villus Sampling

13. Auditable standards

- Rate of pregnancy loss at any gestation after a procedure.
- Rate of pregnancy loss less than 24^{+0} weeks after a procedure.
- Rate of pregnancy loss within 14 days of procedure.
- Local cytogenetic laboratory culture failure rates for amniocentesis and CVS.
- Proportion of procedures requiring more than one needle insertion.
- Proportion of procedures with failure to obtain an adequate sample.
- Complication rates ('bloody' tap, amniotic fluid leakage).
- Maintenance of a register of invasive diagnostic procedures to facilitate audit. Audit should be performed annually and the results made accessible to patients.
- Rate of anti-D prophylaxis for women who are RhD-negative undergoing amniocentesis or CVS.

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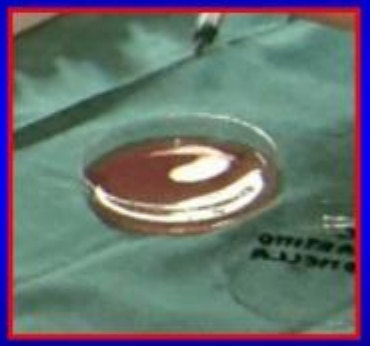
INVASIVE PRENATAL DIAGNOSIS PROCEDURE RELATED



FETAL LOSSES ~ 1%

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THE DEBATE ON ASSESSMENT OF FETAL LOSSES AFTER INVASIVE PROCEDURES AND INVASIVE PROCEDURES- RELATED

- 60 days after the procedure…..
- 30 days after…..
- 4 weeks after…..
- After 24 weeks….
- Losses because of PROM…..
- Perinatal assessment…..

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PRENATAL DIAGNOSIS
Prenat Diagn 2009; **29**: 606–612.
Published online 17 March 2009 in Wiley InterScience
(www.interscience.wiley.com) **DOI:** 10.1002/pd.2256

Antibiotic Prophylaxis before second-trimester Genetic Amniocentesis (APGA): a single-centre open randomised controlled trial

Claudio Giorlandino[1]*, Pietro Cignini[1], Marco Cini[2], Cristiana Brizzi[1], Ornella Carcioppolo[1], Vincenzo Milite[1], Claudio Coco[1], Paolo Gentili[1], Lucia Mangiafico[1], Alvaro Mesoraca[3], Domenico Bizzoco[3], Ivan Gabrielli[3] and Luisa Mobili[1]

PRENATAL DIAGNOSIS
Prenat Diagn 2010; **30**: 188.
Published online in Wiley InterScience
(www.interscience.wiley.com)

CORRESPONDENCE

Antibiotic prophylaxis before second-trimester genetic amniocentesis

Dear editor,

I am quite sure that the paper by Giorlandino *et al.* (2009) will elicit an interesting debate, both on the core message of the study and its conduct. The study conveys a new unexpected message and its potential impact requires a careful scrutiny.

The first relevant question is about the possible conflict of interest between the authors of this scientific work and the private Artemisa Medical Group directed by the principal author himself. To clear this possible conflict, it is of relevant importance to know if the ethical

We understand that a complete follow-up to term would have been impossible, yet a longer follow-up in pPROM pregnancies alone would have helped much to provide a more complete and reliable assessment of amnio complications. It is a pity that the organization of the study was able to provide short term follow-up for thousands of patients and missed the opportunity to provide relevant information for 10–15 patients who suffered major complications of amniocentesis. We read that only 1 in 12 and 1 in 14 of pPROM <20 weeks of gestation ended in fetal death: this is a bizarre low

E. Ferrazzi[17]

NEED FOR SEVERAL NEEDLE INSERTION

Table III. Needle punctures required for successful amniocentesis by primary author and by residents and fellows under guidance of primary author

		Needle punctures required							
		One			*Two*			*Three*	
		Tinged/Bloody			*Tinged/Bloody*			*Tinged/Bloody*	
Case	*No.*	*No.*	*%*	*No.*	*No.*	*%*	*No.*	*No.*	*%*
Author									
912-1000	77	12	15.6	2	1	50.0	1	0	—
1001-2000	919	112	12.2	36	21	58.3	11	8	72.7
2001-3000	865	90	10.4	13	1	7.7	0	—	—
3001-4000	907	68	7.5	6	3	50.0	1	1	100.0
4001-4592	544	13	2.4	21	1	5.3	0	—	—
Total	3312	295	8.9	78	27	34.6	13	9	69.2
Residents or fellows									
912-1000	6	0	—	3	1	33.3	0	—	—
1001-2000	30	2	16.7	4	3	75.0	0	—	—
2001-3000	117	19	16.2	5	3	60.0	0	—	—
3001-4000	80	6	7.5	5	3	60.0	1	0	—
4001-4592	26	1	3.8	1	1	100.0	0	—	—
Total	259	28	10.8	18	11	61.1	1	—	—

Incidence of blood-tinged or bloody amniotic fluid appearance with single puncture amniocentesis decreases with experience ($P < .0011$).

Second procedures were performed by the senior operator because of failure of fellows

Horger, Am J Ob Gyn 2001

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OTHER PROBLEMS.....

- Prevention of accidental punctures
- Prevention of long term sequelae
- Risks related to psychological and organizational aspects

ISPELS
Istituto Superiore Per La Prevenzione E La Sicurezza Del Lavoro
Linee Guida Per Gli Interventi Di Prevenzione Relativi Alla Sicurezza E All'igiene Del Lavoro Nel Blocco Parto"
GynecoAOGOI 2006
ITALIA

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RESOLUTION OF PROBLEMS...

- Subspecialty in Maternal Fetal Medicine after OB/Gyn specialty (USA AND UK, not available in all places)
- Training as fellow in a MFM department
- Performing procedures on a phantom (simulation model)
- Performing procedures under guidance
- To quantify the exact number of procedures before starting in autonomy
- Continuous audit
- Continual review of certified operators

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NUMBER OF PROCEDURES BEFORE STARTING INDEPENDENTLY

- Dutch Society of Obstet Gynecol.: at least 30 guided- procedures before starting (1997)
- Società Italiana di Ecografia Ostetrica e Ginecologica: no quantification of the number of procedures necessary under guidance, but some experience requested (SIEOG 2006)
- Great Britain: at least 30 guided- procedures in a year for CVS or amnio before starting (RCOG 2010)

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Chorionic villus sampling: technique and training

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Current Opinion in Obstetrics and Gynecology 2010, 22:146–151

(1) The MFM fellows are required to complete their 2nd year prenatal genetics rotation, which introduces them to appropriate aneuploidy screening and diagnostic counseling.

(2) The fellow is required to obtain proficiency in ultrasound-guided transabdominal percutaneous procedures, including amniocentesis and fetal umbilical blood sampling procedures. This can be done concurrently with step 3 (see below).

(3) The fellow is responsible for participating and directly assisting (as 'first assist') a trained CVS provider in at least 50 CVS procedures. This will introduce the fellow to both transabdominal and transcervical techniques. This observational period introduces the fellow to the CVS 'set-up', proper evaluation of uterine position in relation to bowel and bladder, assessment of placental position and approach (transcervical vs. transabdominal), proper techniques of needle/catheter entrance, correct visualization of the needle/catheter, and optimal ways to hold the transducer for accurate ultrasound guidance. Finally, the observational period is important for developing proper bedside conversational technique to put the patient at ease and to answer the patient's questions regarding postprocedure recovery and side effects.

(4) Prior to performing CVS on ongoing pregnancies, the fellow is encouraged to perform transcervical CVS procedures on consenting patients undergoing pregnancy termination in the Stanford Division of Family Planning.

(5) Following completion of these preparatory steps, the fellow will be allowed to directly perform supervised transcervical and transabdominal CVS procedures on ongoing pregnancies in the Stanford Perinatal Diagnostic Center.

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June 2010

Amniocentesis and Chorionic Villus Sampling

8. What is required for training and maintaining good practice in amniocentesis or CVS?

Operators carrying out unsupervised amniocentesis and CVS should be trained to the competencies expected of subspecialty training in maternal and fetal medicine, the RCOG Fetal Medicine Advanced Training Skills Module (ATSM) or other international equivalent.	✓
Clinical skills models, assessment of interaction with patients and supervised procedures should be an integral part of training.	C
Competency should be maintained by carrying out at least 30 ultrasound guided invasive procedures per annum.	✓
Units and operators should carry out continuous audit of frequencies of multiple insertions, failures, bloody taps and post procedure losses.	✓
Very experienced operators (more than 100 per annum) may have a higher success rate and a lower procedure-related loss rate. Occasional operators who perform a low number of procedures per annum may have increased rates of procedure-related loss.	C
Further opinion should be sought from a more experienced operator if difficulties are anticipated or encountered.	✓
Expert opinion suggests that an operator's competence should be reviewed where loss rates appear high and audit should certainly occur where they exceed 4/100 consecutive amniocenteses or 8/100 CVS.	✓

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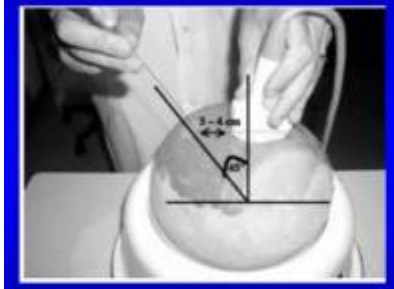
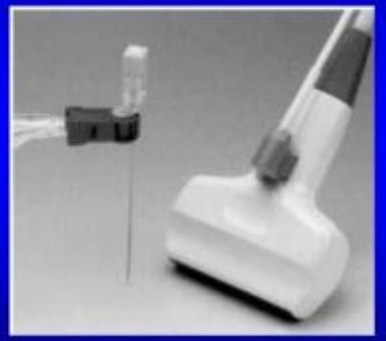
Ultrasound Obstet Gynecol 2002; 19: 274–277

Teaching ultrasound-guided invasive procedures in fetal medicine: learning curves with and without an electronic guidance system

J. NIZARD*, M. DUYME* and Y. VILLE*

*Fetal Medicine Unit, Paris-Ouest University, CHU, Poissy, France





The quality of the procedures increased overtime for all the trainees

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Amniocentesis and Chorionic Villus Sampling

Operator experience, as well as technique, may be important. Results from a study in which the majority of amniocenteses were undertaken by a single operator were compared with those of an occasional operator. With the former, success at the first attempt occurred in 94% of amniocenteses, with 3% of bloody taps, compared with 69% and 16%, respectively, for the latter.[16] Maternal contamination rates are lower when practitioners perform greater numbers of amniocentesis.[16] Studies comparing very experienced practitioners (more than 100 procedures per annum) with less experienced practitioners have shown substantial differences in outcome, with a six- to eight-fold increase in loss rates associated with less experience.[17,18]

Evidence level 2+

A Medical Research Council (MRC) trial found no clear evidence that over the course of the trial (4 years) increased operator experience improved safety of CVS.[19] However, each operator was required to perform at least 30 procedures before participation.

Adequate training and maintenance of skills are important. Ultrasound skills for performing invasive prenatal procedures are greater than those required for the completion of the RCOG specialist training logbook. Specific training in invasive diagnostic procedures will include ultrasound training beyond this level. Best practice requires ultrasound training to the level of the current RCOG subspecialty training in maternal and fetal medicine, ATSM in fetal medicine or equivalent.

Before undertaking procedures on women, consideration should be given to initial training using a clinical skills model. Several suitable models have been constructed and some of these validated.[20] Pittini *et al.* used a well-validated educational approach that included examination of patient interactive skills.[21] They demonstrated improved performance among all levels of trainees but particularly those with the least experience before the training, suggesting an ability to shorten the learning curve. Nizard *et al.* suggest that between 50 and 100 procedures are required to be undertaken before there is no further improvement.[22]

Evidence level 2+

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Amniocentesis and Chorionic Villus Sampling

Postgraduate training is moving to competence-based assessments rather than adherence to a particular numerical goal and no concrete data exist on the number of supervised prenatal invasive procedures necessary before competence is gained. Amniocentesis and CVS procedures are practical skills and trainees will achieve competence at different rates. Individual centres should agree to a training and assessment process that is open and transparent, and with a clearly responsible trainer. Local deaneries and NHS trust clinical governance systems should have a role in ensuring quality training.

Although it is not currently possible to make evidence-based recommendations on the annual number of procedures required to maintain competency, an arbitrary number of at least 30 ultrasound-guided invasive procedures per annum is reasonable. This number should be feasible in most clinical settings in the UK. Operators performing less than this number should ensure that they have audit processes in place to provide robust evidence of safety.

Competence is best assessed through continuous audit of complications such as 'need for second insertion' and 'miscarriage rate'. The 95% confidence intervals for complications from experienced operators[17] indicate that 'second insertion' may be acceptable in, at most, 7/100 consecutive amniocentesis cases. Pregnancy loss should not exceed 4/100 amniocenteses. Higher numbers of complications may be an unfortunate 'cluster' or consequence of high background risk of miscarriage. Nevertheless, where loss rates exceed these limits, an independent review of the operator's skills should be carried out.

Comparable numbers for CVS are different because of the higher background risk of miscarriage. Also, CVS is often performed in the presence of increased nuchal translucency, cystic hygroma, fetal anomalies or genetic conditions, most of which are associated with a higher spontaneous miscarriage rate. The Cochrane Review quotes CVS sampling failure between 2.5% and 4.8% and spontaneous miscarriage rate of 3% after trans-abdominal CVS in the Danish trial and 7.9% in the MRC trial.[19] If one accepts a 3% sampling failure rate and a 3% pregnancy loss as the 'gold standard', an audit of practice should be carried out when either five sampling failures or eight miscarriages occur in 100 consecutive cases.[5]

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OUR EXPERIENCE in CAGLIARI AMNIOCENTESIS

- Invasive procedures were performed earlier on malformations and voluntary terminations (information and consent requested)
- In the beginning, I learned invasive procedures (amniocentesis) in 1980 with senior tutor
- Free hand technique and US guidance
- For subsequent operators, starting as first assistant
- Then guided-procedures by the senior operator

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OUR EXPERIENCE in CAGLIARI

TC- CVS - 1982

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OUR EXPERIENCE in CAGLIARI CHORIONIC VILLI SAMPLING

- I began invasive procedures (TC-CVS) in 1982
  - In Paris by TC biopsy forceps
  - In Cagliari by TC biopsy forceps in TOP and malformations
- Began TA- CVS free-hand technique in 1985 during amniocentesis, voluntary terminations and malformations

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TRAINING INVASIVE PROCEDURES

By Senior tutor supervision

Following a period as "first assistant" in invasive procedures

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TRICKS and SUGGESTIONS FOR TA- CVS

- Initially learn with 18 gauge needle *(instead 20g needle)*
- Starting with 13 weeks fetuses
- First attempts during 2nd trimester amniocentesis
- Learning with voluntary termination cases

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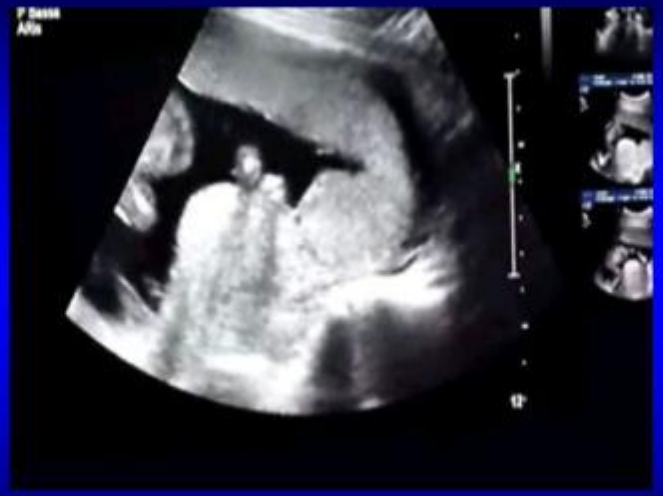

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TEACHING CHORIONIC VILLI SAMPLING PERSONAL EXPERIENCE

- 11 regional fellows
- 44 Italian fellows
- 52 foreign fellows*

*Of whom, 18 fellows from the USA, mostly for TA- CVS