# Evolution of management of pregnancies at-risk for haemophilia in France in the last ten years: impact of non-invasive foetal sex determination

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## Introduction

•Management of pregnancies at-risk for haemophilia was traditionally based on ultrasound and/or invasive prenatal diagnosis (PND). PND was generally offered to families with severe haemophilia and mainly based on chorionic villus sampling (CVS) for foetal karyotype to determine sex and if the foetus was a male to seek for familial mutation. Alternatively, less invasive amniocentesis was proposed in cases of *de novo* mutation as the risk of recurrence is low (mosaic and/or germinal mosaicism).

•Overall, foetal sex determination is a key point to manage and guide the offer of invasive testing in pregnancies with a male foetus.

•Non invasive prenatal diagnosis (NIPD) for fetal sex determination on maternal blood has been introduced as a routine test in France in 2001. We present here data of 10 years of management of pregnancies of carriers at-risk for haemophilia in France.

## Management of Prenatal Diagnosis of pregnancies at-risk for haemophilia in France in 2012

Fetal sex determination on maternal blood ≈10 SA

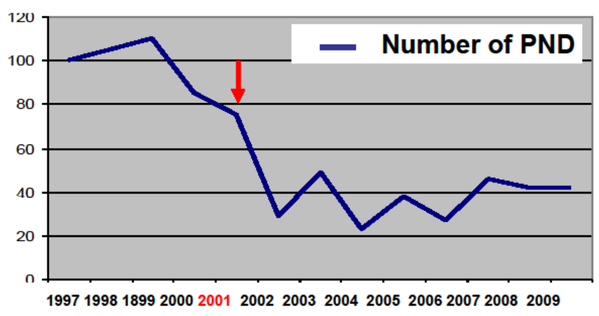
male fetus — female fetus

Prenatal Diagnosis — Ultrasound control

Chorionic villi = 12 SA — Amniotic fluid = 18 SA

All data concerning prenatal diagnosis are notifiable and are collected by the *Agence de la Biomédecine*.

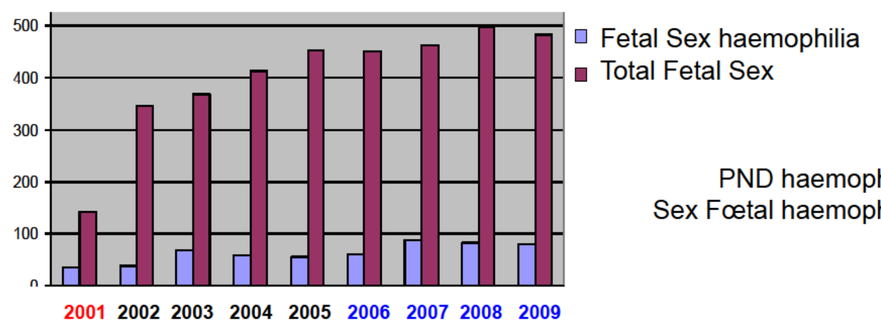
## Evolution of Prenatal Diagnosis Over 10 years




•2001 : Introduction of NIPD on maternal blood.
•Since the 1st year a 25% decrease of PND is observed.
•Since 3 years the number of PND is stable at about n=40+/-5.

•Fetal sex for haemophilia is about 10% of total fetal sex in maternal blood.

## Fetal Sex haemophilia / Total Fetal Sex by NIPD




•Before 2001, average of PND was n≈100 ➔ since 2001 only male fetuses are expected that to say n=50 PND in France. However this number is 20% less, (n=40).

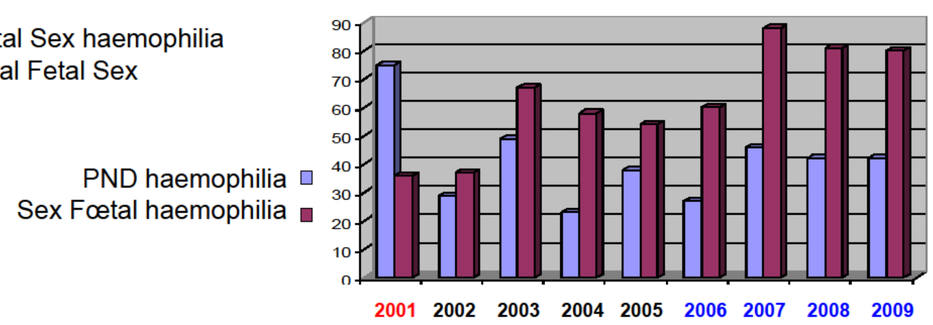
•*Is there a bias on sex ratio male versus female?*

It is rather a positive development in the perception of management of the disease.

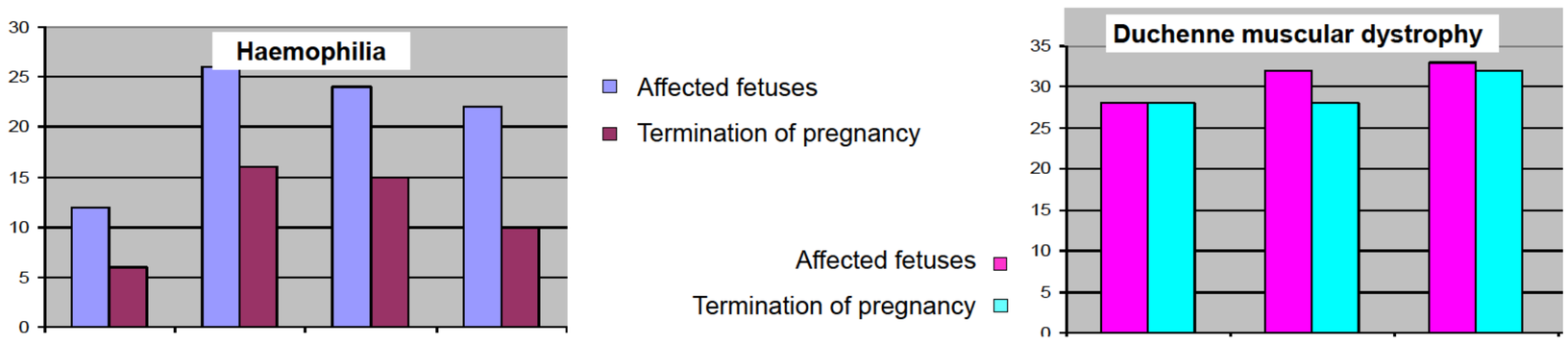
•It tooks 5 years, 2001-2006, to gain confidence in the method when 50% were achieved.

•Today most pregnant carriers benefit from this approach but 40% of them choose for PND.

## PND for haemophilia/ Fetal sex by NIPD




## Followed issues




In France 40% of haemophila carriers choose for PND of which only 50% of women with affected foetuses asked for termination of pregnancy (compared to nearly 100% for Duchenne muscular dystrophy).
This attitude is probably related to the newly positive perception of management of haemophilia. But this is also the wishes of patients and physicians to help appropriate planning of the mode and place of delivery for parents who are unwilling to accept the risk of fetal loss associated with earlier prenatal testing. If a fetus is unaffected, labor and delivery can be managed without any restrictions in local maternity units.

## Conclusion

Next step is moving towards complete NIPD of haemophilia itself, which is the major challenge. But it remains difficult to detect foetal alleles that are inherited from carrier mothers even using the new technologies as recently described, (Tsuyi et al Blood 2011).

Clinical studies are currently in progress in France to evaluate new strategies for the management of pregnant women with *de novo* haemophilia, based on maternal blood examination.

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