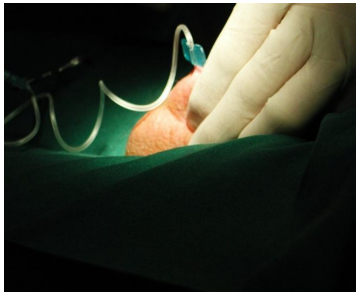
UMC St Radboud

# Epididymal "na-zaat": follow-up of the children

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**IVF-arts**
**UMC St Radboud Nijmegen**

# What will I tell you?

- PESA
  - When?
  - How?
- TESE
  - When?
  - How?
- History
- Follow-up
  - How?
  - Results

# PESA, MESA, TESE

- PESA: Percutaneous Epididymal Sperm Aspiration

- MESA: Microsurgical Epididymal Sperm Aspiration

- TESE: TEsticular Sperm Extraction

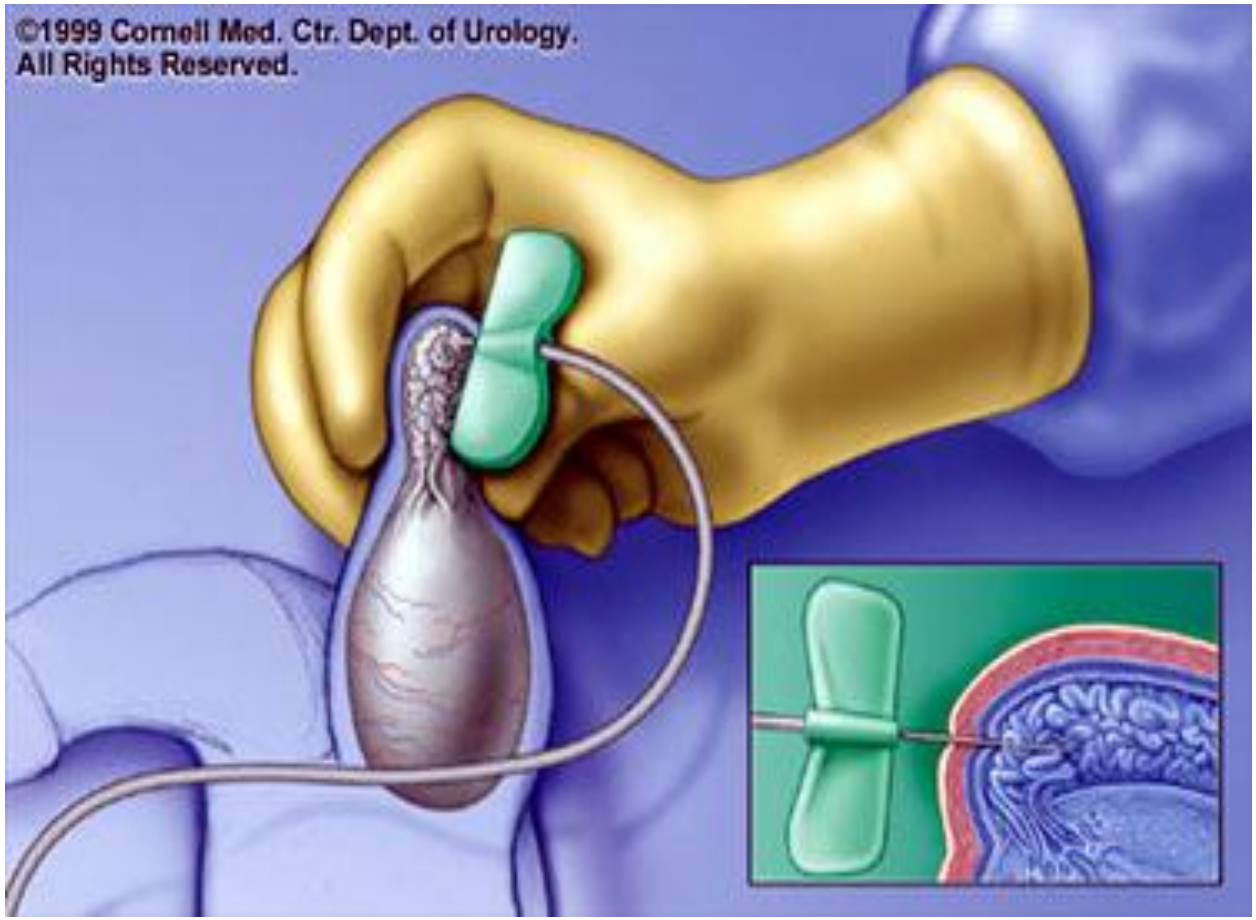
# When PESA?
## (indications)

- Obstructive azoöspermia; normal spermatogenesis
- Anamnesis (vaso-vaso, CBAVD, operations)
- Testisvolume > 15 cc
- FSH < 10

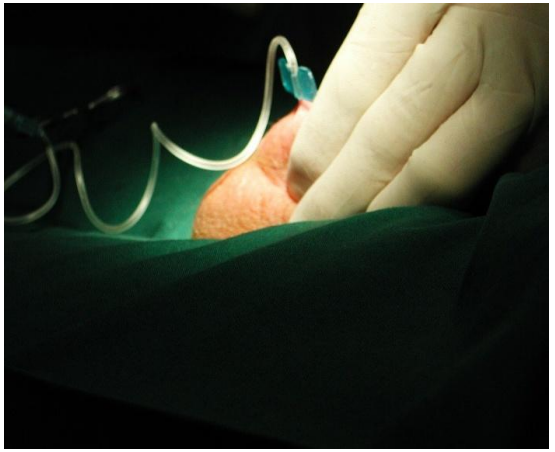
# When no PESA?

- Same protocol as IVF and ICSI
- DNA-deletion on Y chromosome
- Chromosome abnormality of the man

# PESA-procedure



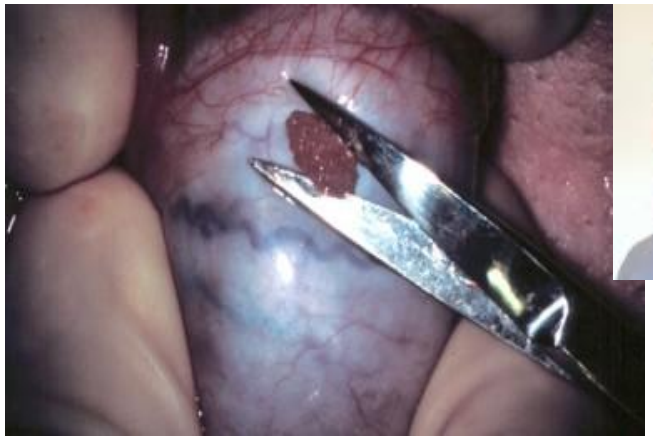
# PESA-procedure



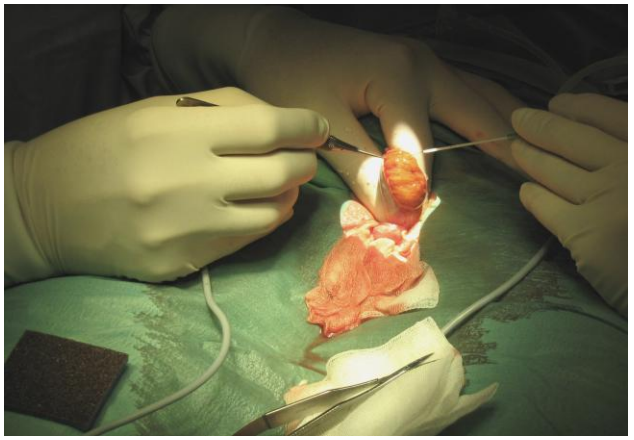
# When TESE?
## (indications)

- Non-obstructive azoöspermia; testicular failure
- In cases of azoöspermia with PESA
- Anamnesis: often not obvious / cryptorchism
- Testisvolume < 15 cc
- FSH > 15

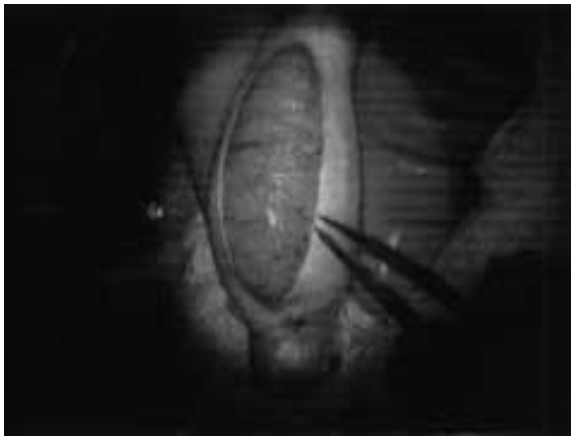
# TESE procedure



H. Tournaye: multiple biopsies

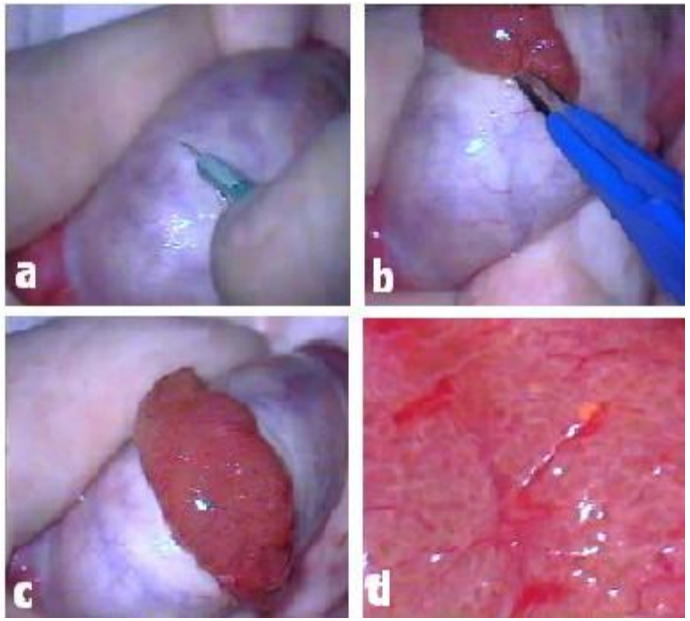


P. Schlegel: open procedure



S. Silber: one "big" biopsy

# TESE-procedure

# "History"

- 1978: Louise Brown born, first IVF-baby in England
- 1983: first IVF-baby in The Netherlands
- 1991: first ICSI-baby in Belgium,
- 1994 first ICSI-baby in The Netherlands
- 1996: moratorium in The Netherlands on ICSI with surgical retrieved sperm
- 2002: "first" PESA-baby in The Netherlands
- 2008: "first" TESE-baby in The Netherlands

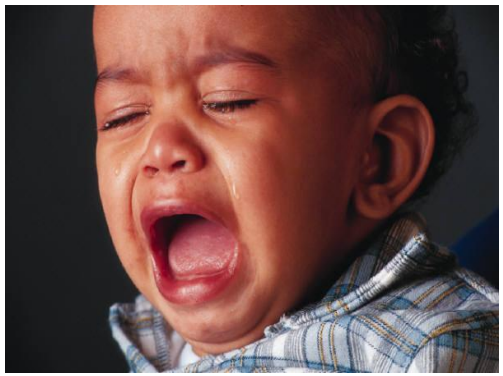
# "History" of moratorium

- 1996: moratorium in The Netherlands on ICSI with surgical retrieved sperm
  - Safety of sperm
  - Safety of the children


- 2001: no moratorium, under conditions
  - Protocol of CCMO (Central Committee on Human Research)

# Protocol CCMO

- Obstructive azoospermia
- Epididymal sperm
- Follow-up of the children



# Follow-up

- Studygroup: **PESA** children
  - from Nijmegen, Utrecht, Rotterdam, Maastricht, Leiderdorp (MCK), Amsterdam (VU)
  - born between Jan 2002 and May 2008

- Control groups: **IVF** and **ICSI** children from UMCN
  - born between June 1995 and May 2007

# How?

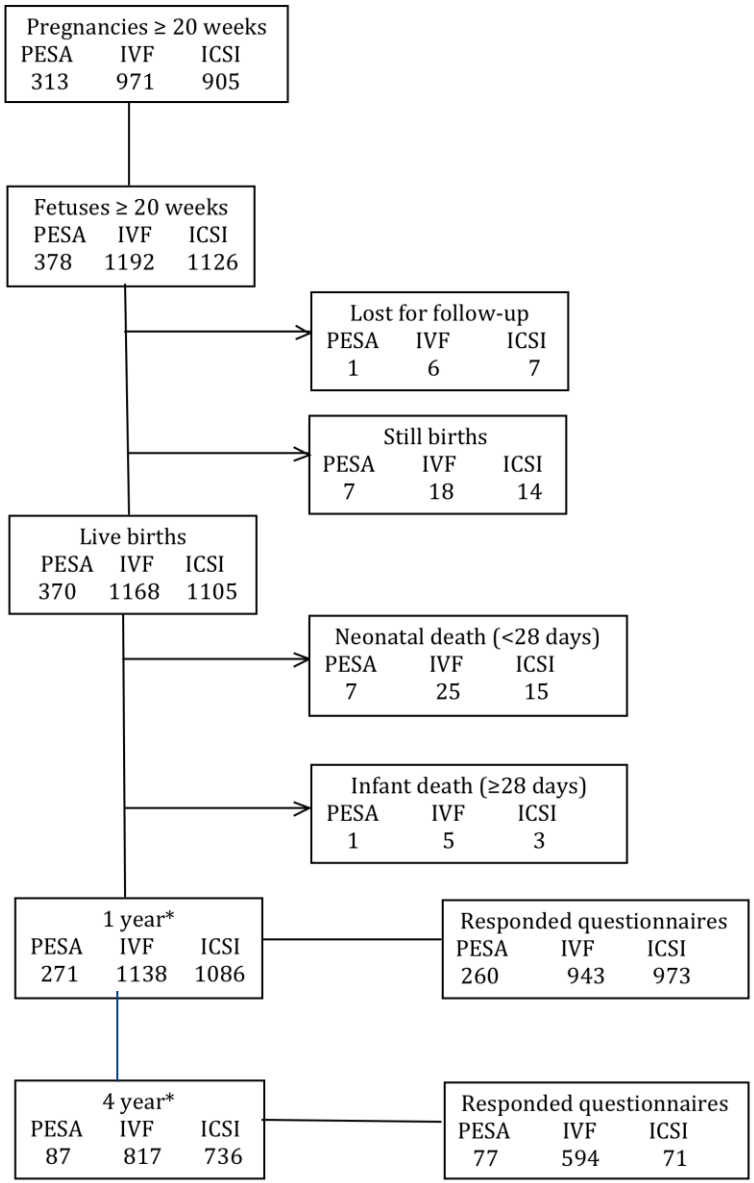
## PESA children:

- Questionnaires at birth, 1 year and 4 years
- Assesment at 2 years and 4 months (or later)
  - Paediatric physical therapist
  - Child psychologist
  - Speech and language therapist
  - Medical doctor

## IVF and ICSI children

- Questionnaires at 1 year and 4 years

# Flow chart




Flow chart of all pregnancies ≥ 20 weeks with delivery between January 2002 and May 2008 for the PESA children and between June 1995 and May 2007 for the IVF and ICSI children.
*reached the age of 1 year respectively 4 years before May 2008

# Live and still births, neonatal and infant deaths (fetuses ≥ 20 weeks)

| | PESA | | | IVF | | | ICSI | | |
|---|---|---|---|---|---|---|---|---|---|
| | Singletons | Multiples | Total | Singletons | Multiples | Total | Singletons | Multiples | Total |
| Total live births and still birth* | 247 | 130 | 377 | 744 | 442 | 1186 | 679 | 440 | 1119 |
| Still births | 4 (1.6%) | 3 (2.3%) | 7 (1.9%) | 11 (1.5%) | 7 (1.6%) | 18 (1.5%) | 10 (1.5%) | 4 (0.9%) | 14 (1.3%) |
| Live births | 243 | 127 | 370 | 733 | 435 | 1168 | 669 | 436 | 1105 |
| Early neonatal death (0 - 7 days) | 2 | 2 | 4 | 5 | 17 | 22 | 4 | 9 | 13 |
| Late neonatal death (7 - 28 days) | 0 | 3 | 3 | 2 | 1 | 3 | 1 | 1 | 2 |
| Infant death (28 days – 1 year) | 0 | 1 | 1 | 1 | 4 | 5 | 1 | 2 | 3 |
| Perinatal death** | 6 (2.4%) | 5 (3.8%) | 11 (2.9%) | 16 (2.2%) | 24 (5.4%) | 40 (3.4%) | 14 (2.1%) | 13 (3.0%) | 27 (2.4%) |
| 95% CI[#] | 0.5-4.4 | 0.5-7.2 | 1.2-4.7 | 1.1-3.2 | 3.3-7.6 | 2.3-4.4 | 1.0-3.2 | 1.3-4.6 | 1.5-3.3 |
| Total deaths | 6 (2.4%) | 9 (6.9%) | 15 (4.0%) | 19 (2.6%) | 29 (6.6%) | 48 (4.0%) | 16 (2.4%) | 16 (3.6%) | 32 (2.9%) |
| 95% CI[#] | 0.5-4.4 | 2.5-11.4 | 2.0-6.0 | 1.4-3.7 | 4.2-8.9 | 2.9-5.2 | 1.2-3.5 | 1.9-5.4 | 1.9-3.9 |

* without fetuses lost for follow up; **= still births and early neonatal death together; [#] 95% CI of percentage

# Parental characteristics of live births

| | PESA | | IVF | | ICSI | |
|---|---|---|---|---|---|---|
| | *n/mean* | *%;95%CI/range* | *n/mean* | *%;95%CI/range* | *n/mean* | *%;95%CI/range* |
| Total deliveries | 308 | | 952 | | 888 | |
| Singletons | 243 | 78.9; 74.2-83.5 | 733 | 77.0; 74.3-79.7 | 669 | 75.3;72.4-78.2 |
| Twins | 65 | 21.1; 16.5-25.8 | 219 | 23.0; 20.3-25.7 | 219 | 24.7;21.8-27.6 |
| Maternal age (years)[1] | | | | | | |
| Total | 33.4 | 23.1-41.9 | 34.3 | 21.5-43.5 | 33.4 | 20.7-42.7 |
| Singletons | 33.5 | 23.1-41.9 | 34.6 | 21.5-43.5 | 33.6 | 21.3-42.7 |
| Twins | 33.1 | 23.6-40.8 | 33.5 | 21.5-41.0 | 32.9 | 20.7-41.2 |
| Paternal age (years)[1] | | | | | | |
| Total | 41.1 | 26.8-67.2 | 36.7 | 21.4-61.4 | 36.5 | 22.7-56.8 |
| Singletons | 41.4 | 26.8-64.2 | 36.9 | 21.5-61.4 | 36.6 | 22.7-56.8 |
| Twins | 40.0 | 29.8-67.2 | 36.1 | 21.4-58.9 | 36.1 | 25.6-55.0 |
| Maternal smoking[2] | | | | | | |
| No smoking | 284 | 93.4; 90.6-96.3 | 714 | 90.2; 88.0-92.2 | 720 | 91.5; 89.5-93.5 |
| Smoking | 20 | 6.6; 3.7-9.4 | 78 | 9.8; 7.7-12.0 | 67 | 8.5; 6.5-10.5 |
| Unknown | 4 | | 160 | | 101 | |
| Education mother | | | | | | |
| Low[3] | 46 | 15.2; 11.1-19.3 | 125 | 15.8; 13.2-18.4 | 123 | 15.6; 13.0-18.2 |
| High[4] | 257 | 84.8; 80.7-88.9 | 667 | 84.2; 81.6-86.8 | 665 | 84.4; 81.8-87.0 |
| Unknown | 5 | | 160 | | 100 | |
| Education father | | | | | | |
| Low[3] | 48 | 15.9; 11.7-20.1 | 172 | 21.8; 18.9-24.8 | 159 | 20.2; 17.3-23.1 |
| High[4] | 254 | 84.1; 79.9-88.3 | 616 | 78.2; 75.2-81.1 | 628 | 79.8; 76.9-82.7 |
| Unknown | 6 | | 164 | | 101 | |
| Parity | | | | | | |
| First | 243 | 79.9; 75.3-84.5 | 546 | 69.2; 65.9-72.5 | 599 | 75.7; 72.7-78.8 |
| ≥ Second | 61 | 20.1; 15.5-24.7 | 243 | 30.8; 27.5-34.1 | 192 | 24.3; 21.2-27.3 |
| Unknown | 4 | | 163 | | 97 | |

# Paediatric characteristics of live births

| | PESA | | IVF | | ICSI | |
|---|---|---|---|---|---|---|
| | *n/mean* | *%;95%CI/range* | *n/mean* | *%;95%CI/range* | *n/mean* | *%;95%CI/range* |
| Total | 370 | | 1168 | | 1105 | |
| Singletons | 243 | 65.7; 60.7-70.6 | 733 | 62.8; 59.5-65.6 | 669 | 60.5; 57.6-63.5 |
| Twins | 127 | 34.3; 29.4-39.3 | 435 | 37.2; 34.4-40.1 | 436 | 39.5; 36.5-42.4 |
| Gender | | | | | | |
| Boys | 181 | 49.6; 44.4-54.8 | 565 | 51.9; 48.9-54.9 | 504 | 48.0; 44.9-51.0 |
| Girls | 184 | 50.4; 45.2-55.6 | 524 | 48.1; 45.1-51.1 | 547 | 52.0; 49.0-55.1 |
| Unknown | 5 | | 79 | | 54 | |
| Birth weight (gram) | | | | | | |
| Total | 2983.2 | 500-4840 | 2932.5 | 375-4885 | 2967,6 | 350-5180 |
| Singletons | 3315.6 | 500-4840 | 3271.5 | 375-4885 | 3318.2 | 720-5180 |
| Twins | 2337.1 | 765-4010 | 2359.3 | 385-4055 | 2434.5 | 350-4288 |
| Unknown | 2 | | 19 | | 6 | |
| Birth weight < 1500 g | | | | | | |
| Total | 23 | 6.3; 3.7-8.8 | 42 | 3.7; 2.5-4.8 | 28 | 2.5; 1.6-3.5 |
| Singletons | 3 | 1.2; 0.0-2.7 | 8 | 1.1; 0.3-1.9 | 3 | 0.5; 0.0-1.0 |
| Twins | 20 | 16.0; 9.4-22.6 | 34 | 8.0; 5.3-10.6 | 25 | 5.7; 3.5-8.0 |
| Birth weight < 2500 g | | | | | | |
| Total | 91 | 24.7; 20.2-29.2 | 222 | 19.3; 17.0-21.7 | 225 | 20.5; 18.0-22.9 |
| Singletons | 23 | 9.5; 5.7-13.2 | 43 | 6.0; 4.2-7.7 | 41 | 6.2; 4.3-8.1 |
| Twins | 68 | 54.4; 45.5-63.2 | 179 | 41.9; 37.1-46.7 | 184 | 42.2; 37.5-46.9 |
| Gestational age (weeks) | | | | | | |
| Total | 38.0 | 23.3-42.4 | 38.0 | 21.9-43.1 | 38.2 | 20.4-43.3 |
| Singletons | 39.3 | 23.3-42.4 | 39.3 | 24.6-43.1 | 39.4 | 20.9-43.3 |
| Twins | 35.6 | 27.1-42.1 | 35.7 | 21.9-40.0 | 36.3 | 20.4-40.6 |
| Unknown | 6 | | 133 | | 71 | |
| Prematurity < 37 weeks | | | | | | |
| Total | 84 | 23.1; 18.7-27.5 | 262 | 25.3; 22.6-28.0 | 227 | 22.0; 19.4-24.5 |
| Singletons | 22 | 9.1; 5.4-12.8 | 70 | 10.6; 8.2-12.9 | 46 | 7.3; 5.2-9.4 |
| Twins | 62 | 50.4; 41.4-59.4 | 192 | 51.6; 46.4-56.8 | 180 | 44.3; 39.4-49.3 |

# Major and minor malformations of live born children

| | PESA | | IVF | | ICSI | |
|---|---|---|---|---|---|---|
| | *n* | *%; 95%CI* | *n* | *%; 95%CI* | *n* | *%; 95%CI* |
| Total | 370 | | 1168 | | 1105 | |
| Major malformation* | 13 | 3.6; 1.6-5.5 | 46 | 4.8; 3.4-6.2 | 33 | 3.4; 2.2-4.6 |
| Minor malformation** | 27 | 7.4; 4.7-10.1 | 142 | 14.9; 12.6-17.2 | 147 | 15.2; 12.9-17.5 |
| No malformations | 325 | 89.0; 85.8-92.3 | 766 | 80.3; 77.7-82.9 | 788 | 81.4; 78.9-83.9 |
| Unknown | 5 | | 214 | | 137 | |
| Singletons | 243 | | 733 | | 669 | |
| Major malformation* | 8 | 3.3; 1.0-5.6 | 28 | 4.5; 2.8-6.1 | 18 | 3.0; 1.6-4.4 |
| Minor malformation** | 17 | 7.0; 3.7-10.3 | 92 | 14.6; 11.8-17.4 | 100 | 16.7; 13.6-19.7 |
| No malformations | 217 | 89.7; 85.8-93.6 | 509 | 80.9; 77.7-84.1 | 481 | 80.3; 77.1-83.6 |
| Unknown | 1 | | 104 | | 70 | |
| Twins | 127 | | 435 | | 436 | |
| Major malformation* | 5 | 4.1; 0.5-7.6 | 18 | 5.5; 3.0-8.1 | 15 | 4.1; 2.0-6.1 |
| Minor malformation** | 10 | 8.1; 3.2-13.1 | 50 | 15.4; 11.4-19.4 | 47 | 12.7; 9.3-16.2 |
| No malformations | 108 | 87.8; 81.9-93.7 | 257 | 79.1; 74.6-83.6 | 307 | 83.2; 79.3-87.1 |
| Unknown | 4 | | 110 | | 67 | |

* number of children with one or more major malformations or major and minor malformations; ** number of children with one or more minor malformations and no major malformations

**Table III** Major malformations per study group (%)

| Authors | Major malformations | | | | | Outcome[#] |
|---|---|---|---|---|---|---|
| | ICSI with ejac. sperm | ICSI with epid. sperm | ICSI with testic. sperm | IVF | Natural conceived children | |
| Bonduelle *et al.* | 84/2477 (3.4) | 4/105 (3.8) | 6/206 (2.9) | 112/2955 (3.8) | NA | No statistical difference (ejaculated sperm versus non-ejaculated sperm; testicular sperm versus epididymal sperm; ICSI versus IVF) |
| Källén *et al.* | 139/4248 (3.3) | 5/135 (3.7) | 3/147 (2.0) | 284/ 10 116 (2.8) | NA | No significant difference (between different methods of ICSI; between standard IVF and ICSI)* |
| Ludwig and Katalinic | 248/2944 (8.4) | 1/26 (3.8) | 21/229 (9.2) | NA | 2140/30 940 (6.9) | No influence of sperm origin; increased risk after ICSI compared with natural conceived children[¶] |
| Palermo *et al.* | 33/1774 (1.9) | 4/198 (2.0) | 1/87 (1.1) | 30/1796 (1.7) | NA | No difference in frequency (between IVF and ICSI; between ejaculated, epididymal and testicular sperm) |
| Wennerholm *et al.* | 39/934 (4.2) | 3/69 (4.3) | 0/31 (0.0) | NA | NA | Similar rate in different subgroups |

[#]Outcome of the study as mentioned in article.

*Adjusted for potential confounders: year of birth, maternal age and parity, years of involuntary childlessness and maternal smoking in early pregnancy.

[¶]Included stillbirths.

Ejac., ejaculated; Epid., epididymal; Testic., testicular; NA, not available.

Woldringh GH, Besselink DE, Tillema AH, Hendriks JC, and Kremer JA (2010) **Karyotyping, congenital anomalies and follow-up of children after intracytoplasmic sperm injection with non-ejaculated sperm: a systematic review.** Hum Reprod Update 16,12-19.

# Follow-up outcome of the PESA children at 2 years of age

| | Total | Singletons | Twins |
|---|---|---|---|
| | *n (%)/mean (SD)* | *n (%)/mean (SD)* | *n (%)/mean (SD)* |
| **Bayley score: motor** | | | |
| Normal (> -1 SD) | 105 (75.0) | 70 (77.8) | 35 (70.0) |
| At Risk (-2 < x < -1 SD) | 20 (14.3) | 14 (15.5) | 6 (12.0) |
| Abnormal (< -2 SD) | 15 (10.7) | 6 (6.7) | 9 (18.0) |
| Missing | 9 | 2 | 7 |
| PDI: mean (SD) | 97.6 (21.2) | 99.2 (20.8) | 94.7 (21.7) |
| Student-t test | -1.37, $p = 0.173$ | -0.385, $p = 0.701$ | -1,742, $p = 0.088$ |
| **Bayley score: mental** | | | |
| Normal (> -1 SD) | 132 (95.7) | 82 (96.5) | 50 (94.3) |
| At Risk (-2 < x < -1 SD) | 4 (2.9) | 3 (3.5) | 1 (1.9) |
| Abnormal (< -2 SD) | 2 (1.4) | 0 | 2 (3.8) |
| Missing | 11 | 7 | 4 |
| MDI: mean (SD) | 103.8 (11.6) | 105.1 (11.1) | 101.6 (12.1) |
| Student-t test | 3.811, $p < 0.05$ | 4.271, $p < 0.05$ | 0.930, $p = 0.356$ |
| **CBCL: total problem score** | | | |
| Normal range (< 60) | 123 (93.9) | 73 (93.6) | 50 (94.3) |
| Borderline (60-63) | 2 (1.5) | 1 (1.3) | 1 (1.9) |
| Clinical range (>63) | 6 (4.6) | 4 (5.1) | 2 (3.8) |
| Missing | 18 | 14 | 4 |
| CBCL: mean (SD) | 46.9 (9.5) | 47.69 (9.3) | 45.94 (9.7) |
| Student t-test | -3.642, $p < 0.05$ | -2.196, $p < 0.05$ | -3.030, $p < 0.05$ |
| **Receptive language development (Reynell test)** | | | |
| Normal (> -1 SD) | 132 (94.3) | 81 (93.1) | 51 (96.2) |
| At Risk (-2 < x < -1 SD) | 8 (5.7) | 6 (6.9) | 2 (3.8) |
| Abnormal (< -2 SD) | - | - | - |
| Missing | 9 | 5 | 4 |
| RLDQ: mean (SD) | 100.3 (SD 9.27) | 101.2 (SD 9.91) | 98.7 (SD 8.04) |
| Student t-test | 0.364, $p = 0.717$ | 1.158, $p = 0.250$ | -1.145, $p = 0.258$ |
| **Syntactic development (Schlichting test)** | | | |
| Normal (> -1 SD) | 128 (94.2) | 82 (96.5) | 46 (90.2) |
| At Risk (-2 < x < -1 SD) | 8 (5.8) | 3 (3.5) | 5 (9.8) |
| Abnormal (< -2 SD) | - | - | - |
| Missing | 13 | 7 | 6 |
| SDQ: mean (SD) | 101.7 (SD 10.22) | 103.7 (SD 9.44) | 98.1 (SD 10.68) |
| Student t-test | 1.970, $p = 0.051$ | 3.654, $p < 0.05$ | -1.259, $p = 0.214$ |
| **Lexical development (Schlichting test)** | | | |
| Normal (> -1 SD) | 118 (92.9) | 72 (93.5) | 46 (92.0) |
| At Risk (-2 < x < -1 SD) | 9 (7.1) | 5 (6.5) | 4 (8.0) |
| Abnormal (< -2 SD) | - | - | - |
| Missing | 22 | 15 | 7 |
| LDQ: mean (SD) | 100.9 (SD 11.09) | 103.0 SD 11.65) | 97.6 (SD 9.47) |
| Student t-test | 0.888, $p = 0.376$ | 2.247, $p < 0.05$ | -1.762, $p = 0.084$ |

Bayley, Reynell and Schliching tests: the normal group has a mean ± SD of 100 ± 15. CBCL (=Child Behaviour Checklist ): the normal group has a normal mean ± SD of 50 ± 10. Student's t-test was performed over the means, SD's and numbers of the study group vs the Dutch reference group.
PDI = Psychomotor Developmental Index; MDI = Mental Developmental Index; RLDQ = Receptive language development quotient; SDQ = Syntactic development quotient; LDQ = Lexical development quotient

# Conclusions

- PESA children less minor malformations than IVF en ICSI children
- Follow up of PESA children at 2 years of age reassuring
- Moratorium for epididymal sperm not necessary anymore?
- Cave twins!

# Thank you for your attention!