Ovarian ageing and twinning; epidemiology & endocrinology

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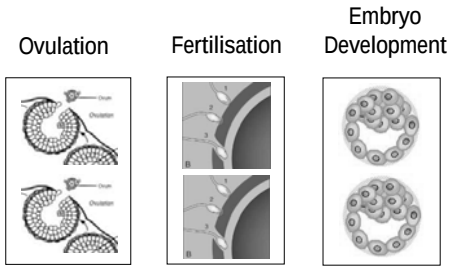
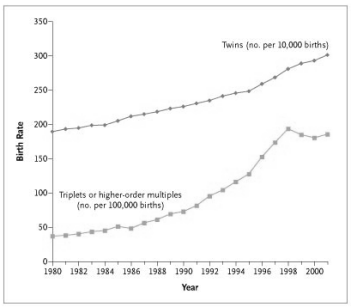
Dizygotic Twinning



Common risk factors for Dizygotic Twinning

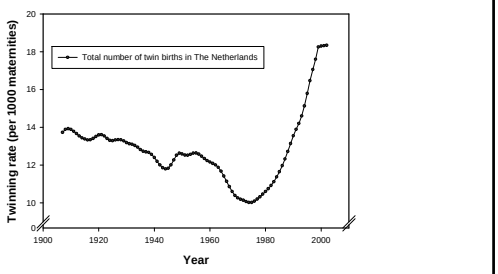
- Artificial
  - Ovulation induction & ART
- Natural
  - Heredity
  - High parity
  - Higher maternal age

Trends in the United States from 1980 to 2001 in the Numbers of Twin Births and Triplet or Higher-Order Multiple Births, Relative to the Total Number of Live Births



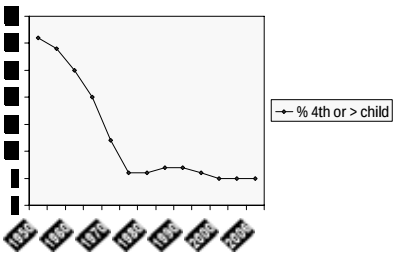
Jain, T. et al. N Engl J Med 2004;350:1639-1645

The NEW ENGLAND JOURNAL of MEDICINE



Orlebeke 2006

Parity in The Netherlands(1950-2006)

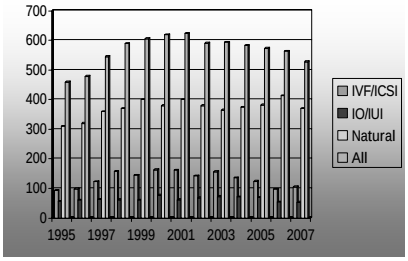


Source: CBS 2007

Method

- Netherlands Perinatal Registry(LVR-2)
- Contains the data of 98 % of all Dutch hospital deliveries from 16 weeks of pregnancy duration including all multiples.
- From 1994 onwards mandatory to register the conception mode(Natural, IVF(ICSI) or OI/IUI).
- 1995-2007
- Boy-girl twin births to ensure dizygosity.
- Assumption: changes in trends of in this twin birth type representative for the all DZ twins.

Numbers of boy/girl twins/100.000 deliveries according to conception type born in The Netherlands(1995-2007)



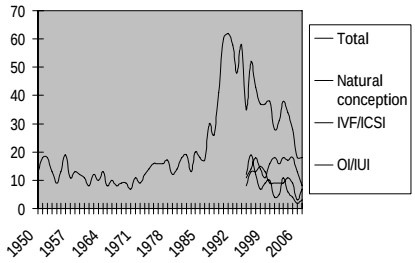
Change in number of Boy/girl twins the Netherlands(1995-2001)

	1995	2001	Increase	Contribution to increase
Natural conception	**578**	**803**	**225(39%)**	**58%**
OI/IUI	**107**	**124**	**17(16%)**	**4%**
IVF/ICSI	**174**	**323**	**149(86%)**	**38%**
All	**859**	**1250**	**391(46%)**	

Change in number of Boy/girl twins the Netherlands(2001-2007)

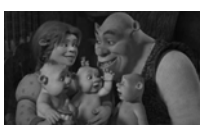
	2001	2007	Change	Contribution to change
Natural conception	**803**	**660**	**- 143(19 %)**	**31 %**
OI/IUI	**124**	**88**	**- 36(29 %)**	**27 %**
IVF/ICSI	**323**	**188**	**- 135(42 %)**	**42 %**
All	**1250**	**926**	**- 324(26 %)**	

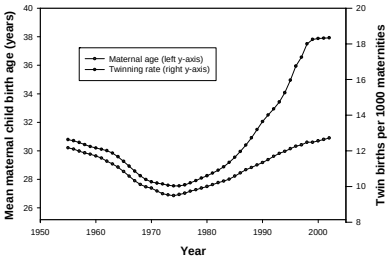
Higher order(>2) pregnancies/100.000 in The Netherlands 1960-2007



Total numbers of triplets in the Netherlands in 2007

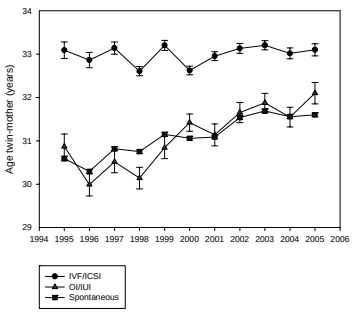
Natural conception	**15**
OI/IUI	**12**
IVF/ICSI	**6**
All	**33**





Orlebeke 2006

Age changes of mothers of DZ twins of various origin in The Netherlands

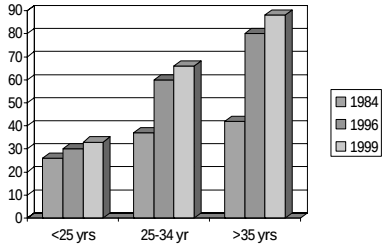


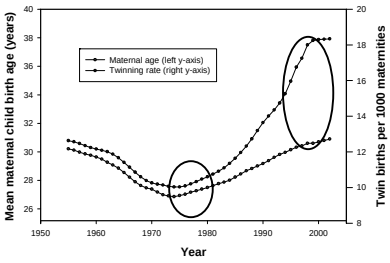
2007

33,5 yrs

31,4 yrs
31,5 yrs

Boy-girl twins/10.000 births
In Netherlands(source CBS)

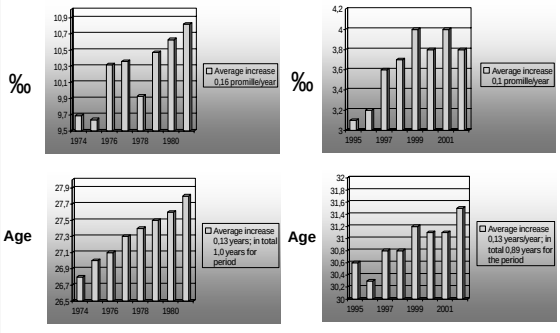




Orlebeke 2003

Maternal age versus natural twinning:
approximately 1 ‰ ↑ / 1 year ↑ of age

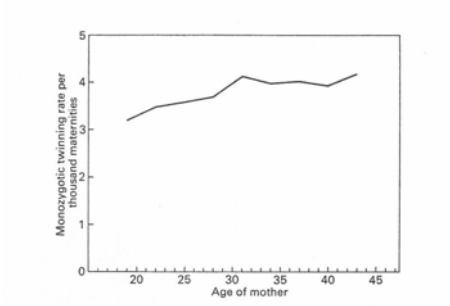
< 1981(CBS) > 1994(LVR)



Potential effects of lower maternal age on twin deliveries

- i.e. :Reduction of 2 years
- Netherlands:150.000-200.000 deliveries/year
- 300-400 natural DZ twin births less(10%)
- 20 neonatal deaths less per year
- 200 NICU admissions less per year

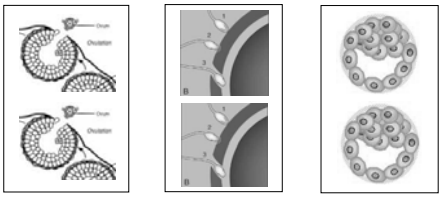
Age changes of mothers of MZ twins



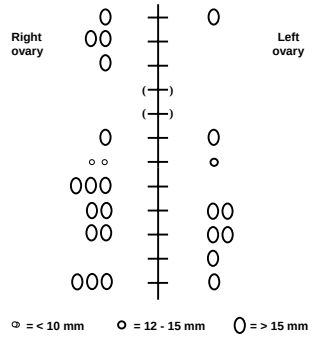
Bulmer 1970

Dizygotic Twinning

Ovulation | Fertilisation | Embryo Development

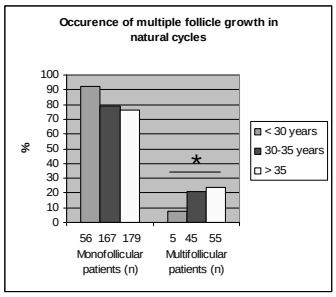


Extreme follicle development monitored by ultrasound on cycle day 12 in mother of familial DZ twin



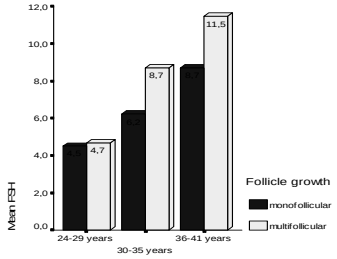
Martin et al Acta Genet Med Gemellol 1991

Age versus occurence of multi follicular development in women undergoing insemination in natural cycles



Beemsterboer et al Hum Reprod 2006

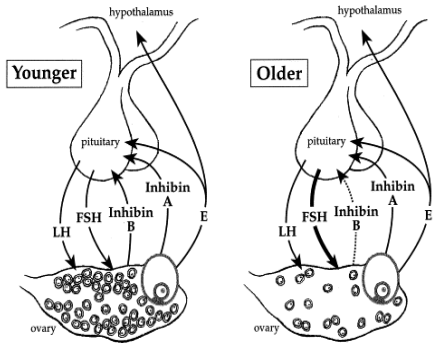
FSH of women with monofollicular or multifollicular growth per age category in in women undergoing natural IUI



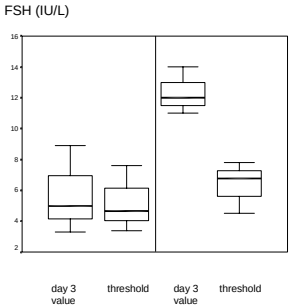
P<0.02

Beemsterboer et al Hum Reprod 2006

Ovarian pituitary interaction with ageing



Day 3 FSH and FSH threshold

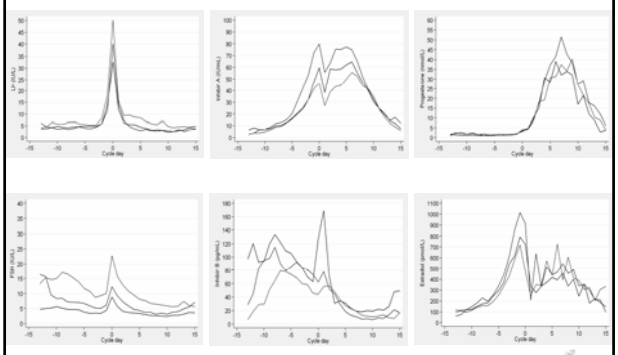


controls

EFP FSH ↑ patients

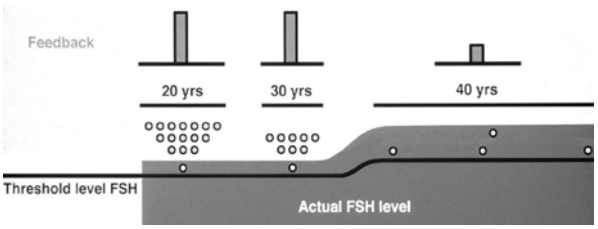
De Koning et al Fertil Steril, 2004

Temporary normalization of elevated basal FSH



De Koning et al Hum Reprod, 2008

Model for DZ twinning with ageing

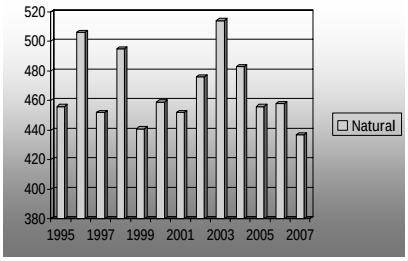


Lambalk Lancet 2001

Conclusions

- In The Netherlands dizygotic twinning rate after IVF/ICSI-OI/IUI strongly increased over the past years with a peak incidence in 2001. Since then it declined.
- The majority of the enormous total increase of DZ twin births came from natural conception
- Increasing maternal age in association with progressive occurence of multiple follicle development is likely to be the largest cause of recent “epidemic” of DZ twinning in The Netherlands
- The endocrinology of reproductive ageing provides plausible clues
- Lowering maternal age could substantially reduce neonatal mortalitity and morbidity by reduction of numbers of natural twin pregnancies

Numbers of natural conception MZ twins /100.000 deliveries in The Netherlands(1995-2007)



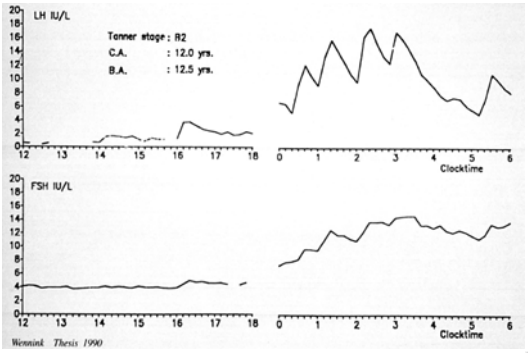
Other conditions

- Recovery from hypothalamic amenorrhea
- Parity

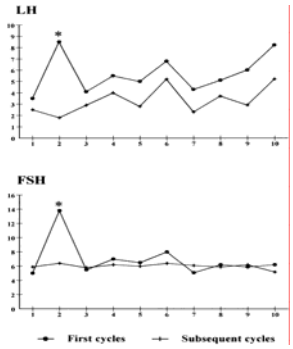
Daily hormones

- High, High group (H,H): elevated FSH in routine work-up and again in the study cycle
- High, Low group (H,L): elevated FSH in routine work-up, but normal in study cycle
- Control group Low, Low (L,L)

De Koning et al Hum Reprod, 2008

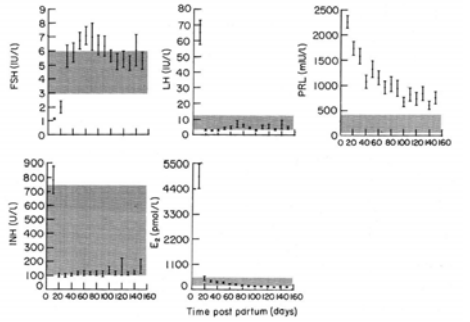


LH & FSH in first LHRH ovulation induction cycle

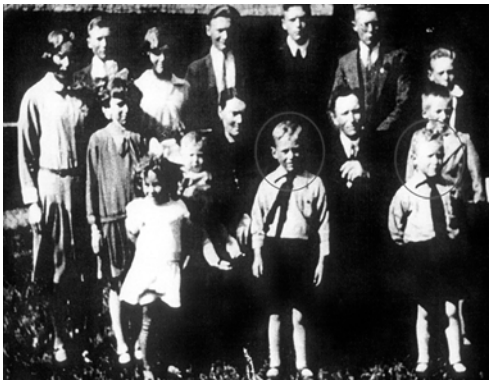


Lambalk & Braat. Mol Cell Endocrinol 1998

Reproductive Hormones during/after Lactation



Burger et al Clin Endocrinol 1994



Conclusions

Elevated FSH seems a key feature of human DZ twinning

Pituitary hypothalamic origin in familial conditions

Ovarian origin in older women

Natural multiple birth

- Familial DZ twinning
  - Hypothalamus/pituitary
  - Ovary
  - Endometrium
- Non familial natural DZ twinning
  - Ageing
  - Other

Conclusions

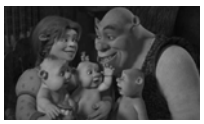
In The Netherlands dizygotic twinning rate after IVF/ICSI-OI/IUI strongly increased over the past decade with a peak incidence in 2001. Since then it is declining

The majority of the enormous total increase of DZ twin births came from natural conception

Increasing maternal age in association with progressive occurence of multiple follicle development is likely to be the largest cause of recent “epidemic” of DZ twinning in The Netherlands

Total numbers of triplets in the Netherlands in 2006

Natural conception	**24**
OI/IUI	**5**
IVF/ICSI	**4**
All	**33**



Twinmother study

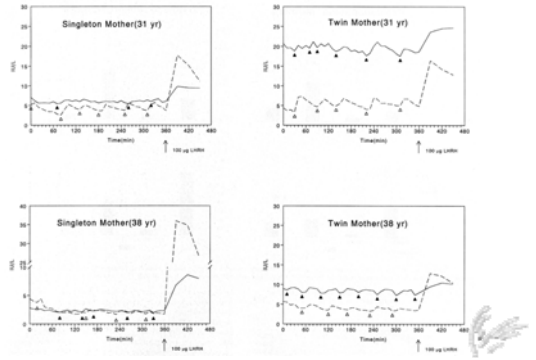
Over the day any FSH value above 10 U/l

	FSH > 10 U/l	FSH < 10 U/l	
DZ Mothers	7	9	16
C Mothers	1	13	14
	8	22	30

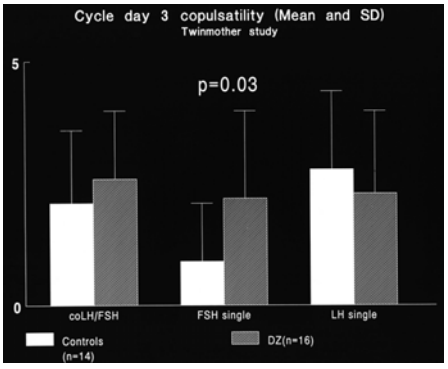
Fisher Exact test: 2-tailed P<0.05

Lambalk et al JCEM 1998

Episodic LH and FSH secretion in mothers with hereditary twinning



Lambalk et al JCEM 1998



Lambalk et al JCEM 1998

566 SEPTEMBER 12, 1964 THE LANCET

Hypothesis

PITUITARY GONADOTROPHIN AND DIZYGOTIC TWINNING

Dizygotic twinning may be explained by multiple ovulation caused by excessive production of gonadotrophin.

Pituitary gonadotrophin levels of women of childbearing age should vary with age, showing an age-distribution similar to that of the dizygotic-twinning rates.

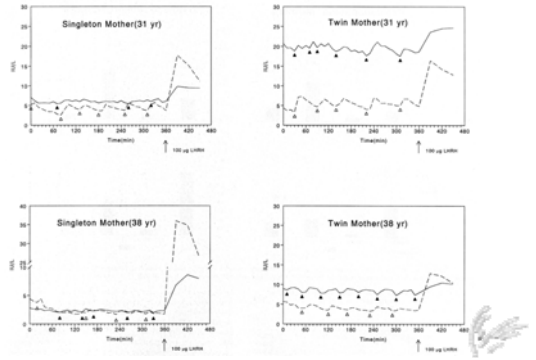
Mothers of dizygotic twins should have higher gonadotrophin levels than mothers of single births.

In essence, what I am suggesting is that dizygotic twinning in human beings may be a visible indicator of excessive maternal pituitary gonadotrophin activity.

New York State Department of Health, Albany, New York

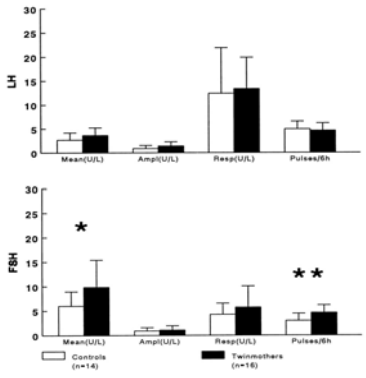
SAMUEL MILHAM, JR. M.D. Albany

Episodic LH and FSH secretion in mothers with hereditary twinning



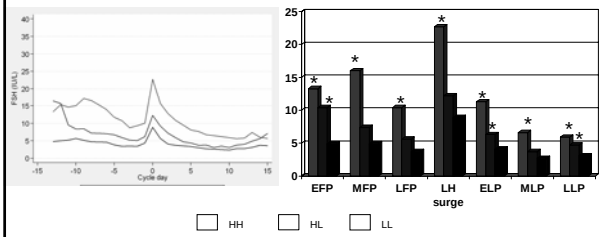
Lambalk et al JCEM 1998

Episodic LH & FSH in DZ twinning



Lambalk et al JCEM 1998

FSH

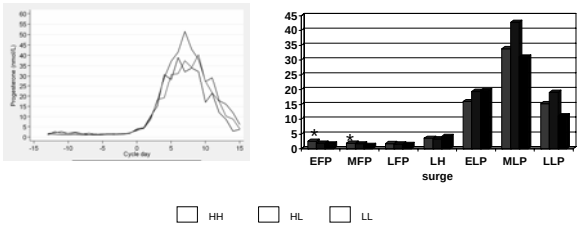


FSH higher in all phases in H,H group

FSH higher in EFP, ELP and LLP in H,L compared with controls

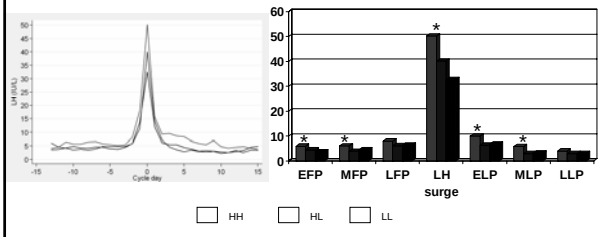
De Koning et al Hum Reprod, 2008

Progesterone



De Koning et al Hum Reprod, 2008

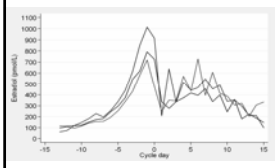
LH

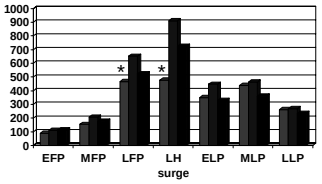


LH higher in H,H group in EFP, MFP, LH surge, ELP, MLP

De Koning et al Hum Reprod, 2008

Estradiol

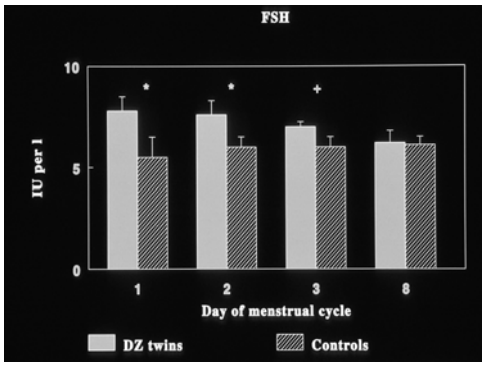




HH HL LL

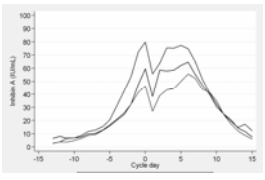
Estradiol lower in H,H group in late follicular phase and LH surge compared to H,L and controls

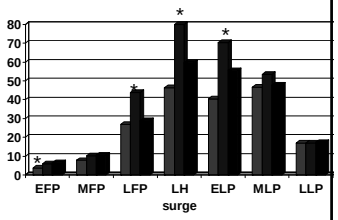
De Koning et al Hum Reprod, 2008



Martin et al Fertil Steril 1984

Inhibin A



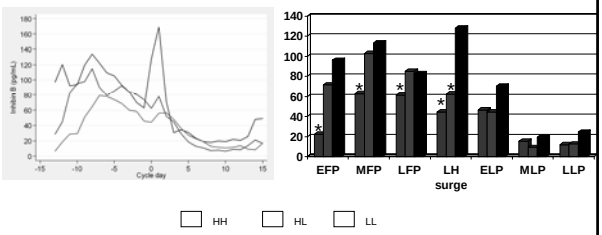


HH HL LL

Inhibin A higher in H,L group in LFP, LH surge, ELF compared to controls

De Koning et al Hum Reprod, 2008

Inhibin B



Inhibin B lower in H,H group in follicular phase and LH peak day compared with controls and H,L

Inhibin B lower in H,L group during LH peak compared with controls

De Koning et al Hum Reprod, 2008

Change in number of Boy/girl twins the Netherlands(2001-2006)

	2001	2006	Change	Contribution to change
Natural conception	**803**	**754**	**- 49(-6 %)**	**22 %**
OI/IUI	**124**	**100**	**- 24(19 %)**	**11 %**
IVF/ICSI	**323**	**177**	**- 146(-45 %)**	**67 %**
All	**1250**	**1031**	**- 219(-16 %)**	

Lambalk et al 2008

Smoking

Higher multiple births are reported in mothers who smoke.

- Olsen et al. (1988)
- Parazzini et al. (1996)
- Murphy et al. (1998)
- Kallen (1998)
- Hoekstra et al (2008)

Total numbers > 2 multiple deliveries according to conception type born in The Netherlands(1995-2007)