Supplemental material

Results from Danish and Finnish questionnaires

Results from the written Danish questionnaire showed a trend in the same direction as the computer assisted telephone interview. Thus, there was an association between consumption of mild analgesics and increased risk of cryptorchdism (although not statistically significant) both when investigating timing and extent of use during pregnancy (Supplemental tables I and II). In Finland, 42.3% (619/1463) of the mothers reported use of mild analgesics, suggesting that the underreporting may not be as severe as in Denmark. The birth prevalence of cryptorchidism in Finland (2.4%) was much lower than in Denmark (9.0%) (Boisen *et al.*, 2004). Thus, a much larger cohort is needed to find a similar number of cases as in the Danish cohort. Nevertheless, there was a trend in the same direction for maternal analgesic use during second trimester (Tables I and II), but we did not find any significant association between maternal use of mild analgesics during pregnancy and the risk of cryptorchidism in the Finnish cohort.

Reference

Boisen KA, Kaleva M, Main KM, Virtanen HE, Haavisto AM, Schmidt IM, Chellakooty M, Damgaard IN, Mau C, Reunanen M et al. Difference in prevalence of congenital cryptorchidism in infants between two Nordic countries. *Lancet* 2004;**363**:1264-1269.

Supplemental table I: Questionnaire data on maternal use of mild analgesics in pregnancy in relation to congenital cryptorchidism in Denmark.

	Prevalence (%)	Cryptorchidism* (n (%))	Normal (n (%))	Fisher's exact (*p*)	OR crude (95% CI)	OR adjusted (95% CI)**	N***
Denmark							
Use of mild analgesics during pregnancy							
No	8.3	51 (70.8)	565 (74.1)	0.58	1.18 (0.69-2.01)	1.36 (0.78-2.36)	834
Yes	9.6	21 (29.2)	197 (25.9)				
Use of mild analgesics during 1st trimester							
No	8.4	57 (83.8)	625 (88.3)	0.33	1.45 (0.73-2.88)	1.69 (0.84-3.42)	776
Yes	11.7	11 (16.2)	83 (11.7)				
Use of mild analgesics during 2nd trimester							
No	8.7	59 (86.8)	622 (87.9)	0.85	1.10 (0.53-2.30)	1.32 (0.62-2.83)	776
Yes	9.5	9 (13.2)	86 (12.1)				

* Testis defined as cryptorchid if it was high scrotal, supra-scrotal, inguinal, and non-palpable.

** Adjusted for gestational age, reported disease, twins, and other medicine use during pregnancy.

***The numbers differ since not all women provided information about the trimester of use.

Supplemental table II: Questionnaire data on extent of maternal use of mild analgesics during pregnancy in relation to congenital cryptorchidism in Denmark.

	Weeks of usage	N*	Cryptorchidism** (%)	OR crude (95% CI)	OR adjusted*** (95% CI)
Denmark					
Mild analgesics	0	623	8.3	1	1
	1-2	101	9.9	1.12 (0.59-2.46)	1.46 (0.70-3.03)
	>2	52	11.5	1.43 (0.58-3.51)	1.64 (0.65-4.14)
Paracetamol	0	657	8.2	1	1
	1-2	87	10.3	1.29 (0.61-2.71)	1.53 (0.72-3.29)
	>2	40	12.5	1.60 (0.60-4.24)	1.76 (0.65-4.81)

* The numbers differ between the different mild analgesics since not all women provided information about duration of use.

**Testis defined as cryptorchid if it was high scrotal, supra-scrotal, inguinal, and non-palpable.

***Adjusted for gestational age, reported disease, twins, and other medicine use during pregnancy.

Supplemental table III: Experimental data from studies on pregnant Wistar dams after intrauterine exposure from GD13-21 (mean ± s.e.m.).

Caesarean section GD21	No. of Foetuses	No. of Litters	Maternal body weight	Adj. maternal body weight	No. Implantations	No. live foetuses	Resorptions in % of implant.	Males in % of total
Control	44	4	316.5±11.5	263.1±10.9	11.3±0.6	11.0±0.4	1.9±1.9	54.4±4.1
150 mg/kg/day paracetamol	59	5	307.8±7.9	241.4±6.4	12.6±0.6	11.8±0.7	4.7±3.0	50.8±5.4
250 mg/kg/day paracetamol	61	5	316.0±15.8	247.0±12.4	12.6±1.1	12.2±1.0	3.1±1.9	59.2±6.8
350 mg/kg/day paracetamol	45	4	297.5±7.9	234.4±6.1	12.3±0.6	11.3±0.8	8.1±4.8	50.0±9.0
Control	72	6	313.2±6.9	250.7±5.0	13.0±0.5	12.0±0.7	7.9±3.7	60.5±5.7
350 mg/kg/day paracetamol	70	6	297.9±10.5	243.4±5.4	10.6±1.9	10.0±2.0	3.5±1.8	51.5±6.0
Control	62	6	285.0±14.5	227.2±9.6	11.8±1.0	10.3±1.6	13.6±8.8	57.3±8.6
150 mg/kg/day acetylsalicylic acid	62	6	291.4±9.6	243.5±7.7	10.0±2.2	8.9±2.4	24.6±14.6	38.4±8.6
200 mg/kg/day acetylsalicylic acid	56	5	301.2±8.5	244.2±3.7	12.4±1.6	11.2±2.1	13.3±7.9	62.4±4.1
250 mg/kg/day acetylsalicylic acid	75	7	295.3±8.4	243.0±5.8	11.7±0.7	10.7±1.1	9.3±5.7	53.0±7.8

Supplemental table IV: Weight and anogenital distance (AGD) for male foetuses after intrauterine exposure of Wistar rats from GD13-21 (mean ± s.e.m.).

Caesarean section at GD21	N	Weight (g)	Weight (% of control)	AGD (units)	AGDi[a] (% of control)
Control	4	3.65±0.11	100±3.0	23.12±0.49	100±1.7
150 mg/kg/day paracetamol	5	3.87±0.10	106.1±2.6	21.08±0.23*	89.5±1.4**
250 mg/kg/day paracetamol	5	3.69±0.07	101.3±2.0	21.15±0.30*	91.3±1.8*
350 mg/kg/day paracetamol	4	3.65±0.10	100.1±2.6	21.44±0.97	92.8±3.8[b]
Control	6	3.37±0.18	100±5.2	22.37±0.44	100±0.61
350 mg/kg/day paracetamol	6	3.33±0.12	98.7±3.6	21.4±0.43*	96±1.09**
Control	6	3.95±0.35	100±8.8	21.01±0.52	100±2.7
150 mg/kg/day acetylsalicylic acid	5	3.57±0.24	90.5±6.0	20.07±0.40	98.4±2.2
200 mg/kg/day acetylsalicylic acid	5	3.48±0.31	88.2±8.0	20.60±0.80	102±2.1
250 mg/kg/day acetylsalicylic acid	7	3.08±0.16**	78.1±3.9	19.42±0.57	99.9±2.2

[a] AGDi is defined as AGD divided by the cube root of the body weight.

*ANOVA followed by Dunnett's test $p < 0.05$.

**ANOVA followed by Dunnett's test $p < 0.01$.

[b] ANOVA followed by Dunnett's test $p = 0.062$.

Supplemental table V: Testosterone in Wistar rat foetuses at GD21 after intrauterine exposure from GD13-21 (mean ± s.e.m.).

Caesarean section GD21	N	Testosterone in testes (ng/testis)	Testosterone production in testes (ng/testes)[a]
Control	4	1.31±0.24	3.76±1.90
150 mg/kg/day paracetamol	5	1.63±0.45	3.88±1.29
250 mg/kg/day paracetamol	5	2.06±0.21	3.58±1.33
350 mg/kg/day paracetamol	3	2.11±0.34	3.35±1.42
Control	6	1.29±0.20	3.15±0.30
350 mg/kg/day paracetamol	6	1.56±0.13	2.43±0.41
Control	6	1.24±0.41	2.12±0.36
150 mg/kg/day acetylsalicylic acid	5	1.94±0.28	1.48±0.24[b]
200 mg/kg/day acetylsalicylic acid	5	0.67±0.22	1.25±0.23*
250 mg/kg/day acetylsalicylic acid	6	1.35±0.27	1.65±0.20[c]

[a] Measurements after 3 hours of incubation.

* ANOVA followed by Dunnett's test $p < 0.05$ when compared with control

[b] ANOVA followed by Dunnett's test $p = 0.065$ when compared with control

[c] ANOVA followed by Dunnett's test $p = 0.077$ when compared with control