Addendum:

Supplementary Table 1: Exclusion criteria

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| Exclusion criteria in PREDICT: |
| 1) age <18 years  2) known allergy to progesterone  3) history of hormone-associated thromboembolic disorders  4) rupture of membranes  5) signs of twin-twin transfusion syndrome  6) fetal reduction  7) known major structural/chromosomal fetal abnormality  8) known/suspected malignancy in genitals/breasts  9) known liver disease  10) women with higher-order multiple pregnancies  11) women who did not speak and understand Danish or German, as appropriate. |
| Additional exclusion criteria in present study: |
| 1) From Austrian cohort  2) Both fetuses or children had died before the age of 18 months  3) Both twins were born with severe malformations  4) The parents did not give consent to further follow-up  5) Emigrated  6) Lost to follow-up  7) Did not respond to any ASQ.  Moreover, children diagnosed with a severe congenital malformation were excluded prior to the analyzes (n=10 for ASQ at 18 months and n=4 for ASQ at 48-60 months). |

Supplementary Table 2: Background characteristics for 530 Danish twin pregnant women:

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Included women from Danish cohort**  **n=427** | **Not included in the follow-up after 18 months\***  **n=103** | ***P*-value for comparison of included and excluded women** |
| **Chorionicity**  Monochorionicity | 46 (10.8) | 15 (14.6) | 0.28 |
| **Maternal age,** mean (SD) | 32.2 (4.0) | 31.8 (4.4) | 0.43 |
| **Fertility treatment,** n (%)  Missing data | 221 (51.8) | 41 (39.8)  2 | 0.04 |
| **Parity**  Nulliparous, n (%) | 231 (54.1) | 46 (44.7) | 0.10 |
| **BMI pre-pregnancy,** median (IQR)  Missing | 22.8 (20.7-25.9)  2 | 23.1 (21.2-27.2)  2 | 0.33 |
| **Smoking at inclusion, n (%)**  Missing | 41 (9.6) | 10 (9.8)  1 | 0.95 |
| **Education score\*\*,** median (IQR)  Missing | 10 (7-10)  13 | 9 (7-10)  16 | 0.11 |
| **Marital status**, n (%)  Living alone  Married/co-living  Unknown | 6 (1.4)  421 (98.6) | 2 (1.9)  100 (97.1)  1 (1.0) | 0.12 |

\*Miscarriage, n=3; Both twins died before 18 months after estimated date of delivery, n=1; At least one parent did not give consent to further follow-up, n=26; Emigrated, n=1; Lost to follow-up, n=1; Did not respond to any ASQ, n=69

\*\* Education score: school and education combined; 4 points = 9 years in school and no or little further education or training, and 11 points = high school and university degree.

Supplementary Table 3: Maternal baseline and pregnancy characteristics and the unadjusted association with ASQ score among twins:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **ASQ at 18 months of age, n=823** | | | **ASQ at 48-60 months of age, n=425** | | |
|  | **n(%)** | **Mean score (SD)** | **Mean difference**  **(95% CI)** | **n(%)** | **Mean score (SD)** | **Mean difference**  **(95% CI)** |
| **Chorionicity**  Monochorionicity  Dichorionicity | 86 (10.4)  737 (89.6) | 179.2 (45.2)  188.7 (38.7) | -8.9 (-20.6;2.9)  0 (reference) | 57 (13.4)  368 (86.6) | 264.6 (26.8)  265.8 (30.2) | -1.2 (-11.2;8.8)  0 (reference) |
| **Maternal age**  < 30 years of age  ≥ 30 years of age | 244 (29.6)  579 (70.4) | 186.8 (39.0)  188.0 (39.7) | 0 (reference)  1.0 (-6.8;8.9) | 127 (29.9)  298 (70.1) | 263.4 (31.4)  266.6 (29.0) | 0 (reference)  3.8 (-3.6;11.3) |
| **Parity**  Nulliparous  Multiparous | 443 (53.8)  380 (46.2) | 187.6 (38.3)  187.8 (40.9) | 0 (reference)  -0.1 (-7.3;7.2) | 249 (58.6)  176 (41.2) | 268.1 (28.9)  262.3 (30.6) | 0 (reference)  -5.3 (-12.2;1.6) |
| **IVF/ICSI**  No  Yes | 567 (68.9)  256 (31.1) | 187.8 (41.6)  187.5 (34.4) | 0 (reference)  -1.1 (-8.4;6.7) | 285 (67.1)  140 (32.9) | 265.6 (29.1)  265.8 (31.2) | 0 (reference)  -0.0 (-7.2;7.3) |
| **BMI**  <30.0 kg/m2  ≥30.0 kg/m2  Missing | 719 (87.4)  100 (12.2)  4 (0.5) | 185.2 (37.9)  204.1 (46.0)  226.3 (29.3) | 0 (reference)  18.8 (7.9;29.7)  - | 395 (92.9)  28 (6.6)  2 (0.5) | 266.2 (29.2)  258.6 (37.6)  260.0 (21.2) | 0 (reference)  -7.5 (-21.3;6.2)  - |
| **Smoking at inclusion**  No  Yes | 747 (90.8)  76 (9.2) | 187.0 (39.4)  194.5 (39.7) | 0 (reference)  8.4 (-3.9;20.7) | 398 (93.6)  27 (6.4) | 266.3 (28.9)  256.7 (39.4) | 0 (reference)  -10.2 (-24.1;3.6) |
| **Education score\***  4-6 points  7-9 points  10-11 points  Missing | 126 (15.3)  269 (32.7)  402 (48.8)  26 (3.2) | 196.5 (39.2)  185.7 (42.6)  186.4 (37.1)  185.2 (39.5) | 9.9 (-0.6;20.3)  -1.7 (-9.9;6.5)  0 (reference)  - | 49 (11.5)  135 (31.8)  223 (52.5)  18 (4.2) | 253.5 (34.9)  266.9 (31.3)  267.6 (27.5)  265.6 (24.8) | -15.4 (-26.4;-4.5)  -1.9 (-9.5;5.7)  0 (reference)  - |
| **Marital status**  Married or co-living  Living alone | 811 (98.5)  12 (1.5) | 187.8 (39.4)  180 (43.5) | 0 (reference)  -6.3 (-36.6;24.1) | 417 (98.1)  8 (1.9) | 265.4 (29.9)  277.5 (17.1) | 0 (reference)  13.1 (-12.0;38.2) |
| **Gender combination**  **Monochorionic**  Girl-girl  Boy-boy  **Dichorionic**  Girl-girl  Boy-boy  Different sex | 44 (5.3)  42 (5.1)  207 (25.2)  170 (20.7)  360 (43.7) | 180.9 (38.9)  177.5 (51.4)  190.7 (36.8)  181.3 (35.3)  191.0 (40.9) | -8.3 (-25.2;8.6)  -13.2 (-30.7;4.2)  0 (reference)  -8.7 (-19.4;2.0)  0.3 (-8.6;9.3) | 31 (7.3)  26 (6.1)  113 (26.6)  68 (16.0)  187 (44.0) | 270.2 (20.3)  258.1 (32.1)  269.9 (25.6)  261.8 (37.0)  264.8 (30.0) | 1.0 (-13.2;15.1)  -12.3 (-27.5;2.9)  0 (reference)  -7.4 (-18.1;3.4)  -5.0 (-13.3;3.3) |
| **Gestational diabetes**  No  Yes | 801 (97.3)  22 (2.7) | 187.7 (39.6)  186.6 (35.2) | 0 (reference)  -1.2 (-23.6;21.4) | 419 (98.6)  6 (1.4) | 265.7 (29.9)  264.2 (22.0) | 0 (reference)  -4.4 (-33.6;24.8) |
| **Hypertension, preeclampsia/HELLP**  No  Yes | 735 (89.3)  86 (10.4) | 187.1 (38.8)  191.7 (45.3) | 0 (reference)  3.7 (-8.0;15.5) | 385 (90.6)  40 (9.4) | 265.7 (30.4)  265.5 (22.8) | 0 (reference)  0.3 (-11.4;12.0) |

\* Education score: school and education combined; 4 points = 9 years in school and no or little further education or training, and 11 points = high school and university degrees.

Supplementary Table 4: Neonatal complications associated with ASQ scores below the standardized cut-off for singletons within the five different domains; fine motor skills, gross motor skills, problem solving, social, and communication – adjusted for gestational age at delivery and maternal educational score:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ASQ scores below the standardized cut-offs | **NICU admittance\***  Yes No OR (95% CI) | **IVH/ROP/NEC\*\***  Yes No OR (95% CI) | **Jaundice**  Yes No OR (95% CI) | **CPAP treatment\*\*\*\***  Yes No OR (95% CI) |
| **ASQ 18 months**  Fine motor  Gross motor  Social  Communication  Problem solving | *n=346 n=477*  108 (31.2) 158 (33.1) 0.9 (0.6;1.4)  126 (36.4) 151 (31.7) 1.3 (0.9;2.1)  82 (23.7) 127 (26.6) 0.7 (0.4;1.3)  269 (77.8) 361 (75.7) 1.1 (0.7;1.8)  118 (34.1) 147 (30.8) 1.1 (0.7;1.7) | *n=16 n=805\*\*\**  6 (37.5) 260 (32.3) 1.1 (0.3; 4.6)  10 (62.5) 267 (33.2) 3.3 (1.1;9.5)  11 (68.8) 198 (24.6) 5.3 (1.5;19.0)  13 (81.3) 615 (76.4) 1.0 (0.2;3.7)  7 (43.8) 258 (32.1) 1.4 (0.4;5.1) | *n=145 n=678*  47 (32.4) 219 (32.3) 1.1 (0.7;1.8)  50 (34.5) 227 (33.5) 1.1 (0.7;1.7)  40 (27.6) 169 (24.9) 1.1 (0.7;1.6)  110 (75.9) 520 (76.7) 0.9 (0.5;1.5)  64 (44.1) 201 (29.7) 1.7 (1.2;2.6) | *n=160 n=663*  45 (28.1) 221 (33.3) 0.9 (0.6;1.2)  53 (33.1) 224 (33.8) 0.9 (0.6;1.5)  41 (25.6) 168 (25.3) 1.2 (0.8;1.7)  120 (75.0) 510 (76.9) 0.9 (0.5;1.5)  53 (33.1) 212 (32.0) 1.1 (0.7;1.5) |
| **ASQ 48 or 60 months**  Fine motor  Gross motor  Social  Communication  Problem solving | *n=167 n=245*  15 (8.6) 10 (4.0) 1.1 (0.3;3.4)  5 (2.9) 11 (4.4) 0.3 (0.1;1.7)  3 (1.7) 2 (0.8) 0.4 (0.1;3.1)  9 (5.2) 10 (4.0) 0.9 (0.2;4.3)  5 (2.9) 3 (1.2) 0.9 (0.1;6.7) | *n=6 n=417*  1 (16.7) 24 (5.8) 3.0 (0.4;20.7)  1 (16.7) 15 (3.6) 4.7 (0.6;33.8)  1 (16.7) 4 (1.0) 20.8 (2.6;167.4)  1 (16.7) 18 (4.3) 3.6 (0.5;25.9)  1 (16.7) 7 (1.7) 10.6 (1.4;82.6) | *n=71 n=354*  6 (8.5) 19 (5.4) 0.5 (0.2;1.4)  3 (4.2) 13 (3.7) 0.6 (0.1;3.1)  2 (2.8) 3 (0.9) 1.0 (0.1;7.9)  4 (5.6) 15 (4.2) 0.7 (0.1;4.6)  3 (4.2) 5 (1.4) 0.6 (0.1;6.1) | *n=86 n=339*  10 (11.6) 15 (4.4) 1.5 (0.6;3.7)  4 (4.7) 12 (3.5) 1.5 (0.4;5.6)  3 (3.5) 2 (0.6) 3.4 (0.5;21.9)  6 (7.0) 13 (3.8) 2.3 (0.8;6.8)  4 (4.7) 4 (1.2) 4.3 (0.8;23.9) |

\*Admittance for at least one week

\*\* Unadjusted due to few cases

\*\*\* Two missing cases on ivh/rop/nec

\*\*\*\*Treatment of at least 24 hours

Supplementary Figure 1:

(n=103)

\*10 children with malformations excluded

\*\* 4 children with malformations excluded

(n=425\*\*)

**with ASQ data at 48 or 60 months**

**Danish children**

)

215

(n=

**months**

**or 60**

**8**

**at 4**

**participants where at least one twin had ASQ data**

**Danish**

\*)

(n=823

**with ASQ data at 18 months**

**children**

**Danish**

)

418

(n=

**18 months**

**ASQ data at**

**participants where at least one twin had**

**Danish**

(n=427)

**Danish participants (mothers)**

**with ASQ data at 18, 48 or 60 months**

(n=212)

**at 48 or 60 months**

**Did not respond to ASQ**

(n=9)

**at 18 months**

**Did not respond to ASQ**

Lost to follow-up, n=1

Did not respond to any ASQ = 69

Emigrated, n=1

Did not give consent to follow-up, n=26

Both twins had severe malformations, n=5

Both twins died, n=1

Miscarriage, n=3

**Excluded for the current study purpose**

(n=147)

**Included in Austria**

)

(n=530

**Included in Denmark**

(n=677)

**Included in the PREDICT trial**

Flowchart of the study population.