Supplemental Table 1. Associations between autism spectrum disorder and maternal or paternal infertility disorders in term birth and singleton subsets, Study to Explore Early Development.

|  |  |  |  |
| --- | --- | --- | --- |
| **Infertility Disorder1** | **Total Sample2** | **Term Births** | **Singletons** |
| **Any maternal infertility disorder3** | **N=262** | **N=212** | **N=226** |
| Total sample, Unadjusted OR (95% CI) | 1.4 (1.1-1.8) | 1.3 (0.9-1.7) | 1.3 (0.998-1.8) |
| Total Sample, aOR4 (95% CI) | 1.4 (1.1-1.9)  | 1.3 (0.95-1.8)  | 1.4 (1.001-1.9)  |
| First Birth, aOR (95% CI) | 1.1 (0.7-1.7) | 1.0 (0.7-1.6) | 1.0 (0.7-1.6) |
| Second or Later Birth, aOR (95% CI) | 1.9 (1.3-2.9) | 1.8(1.1-2.9) | 1.9 (1.2-2.9) |
| **Blocked or damaged tubes**  | **N=33** | **N=23** | **N=24**  |
| Total sample, Unadjusted OR (95% CI) | 2.3 (1.1-4.6) | 2.5(1.1-5.8) | 3.1 (1.3-7.3) |
| Total Sample, aOR (95% CI) |  2.2(1.01-4.7) | 2.3 (1.009-5.7)  |  2.6 (1.04-7-6.6) |
| First Birth, aOR (95% CI) | 1.2 (0.3-4.3) | 2.0 (0.5-8.4) | 1.4 (0.3-5.9 |
| Second or Later Birth, aOR (95% CI) | 3.4 (1.3-9.3) | 3.1 (0.9-10.6) | 4.5 (1.3-15.1) |
| **PCOS5/multiple ovarian cysts**  | **N=79** | **N=62** | **N=66** |
| Total sample, Unadjusted OR (95% CI) | 1.0 (0.7-1.6) | 0.8 (0.5-1.4) | 0.9 (0.5-1.5) |
| Total Sample, aOR (95% CI) | 1.0 (0.6-1.7)  |  0.8 (0.5-1.5) |  0.9 (0.5-1.6) |
| First Birth, aOR (95% CI) | 0.6 (0.3-1.1) | 0.5 (0.2-1.1) | 0.5 (0.3-1.1) |
| Second or Later Birth, aOR (95% CI) | 2.7 (1.2-6.1) | 1.9 (0.8-4.6) | 2.3 (0.96-5.6) |
| **PCOS/multiple ovarian cysts or related symptoms reported6**  | **N=118**  | **N=96**  | **N=101**  |
| Total sample, Unadjusted OR (95% CI) | 0.9 (0.7-1.4) | 0.8 (0.5-1.2) | 0.8 (0.5-1.3) |
| Total Sample, aOR (95% CI) | 1.1 (0.7-1.6)  |  0.9(0.6-1.4) |  0.9 (0.6-1.5) |
| First Birth, aOR (95% CI) | 0.7 (0.4-1.2) | 0.7 (0.4-1.2) | 0.6 (0.3-1.1) |
| Second or Later Birth, aOR (95% CI) | 2.0 (1.1-3.8) | 1.4 (0.7-2.9) | 1.8 (0.9-3.6) |
| **Diminished ovarian reserve7**  | **N=34** | **N=25**  |  **N=23** |
| Total sample, Unadjusted OR (95% CI) | 1.3 (0.7-2.6) | 1.2 (0.6-2.7) | 0.8 (0.3-1.9) |
| Total Sample, aOR (95% CI) | 1.2 (0.6-2.6)  |  1.3 (0.5-3.0) | 0.7 (0.3-1.8)  |
| First Birth, aOR (95% CI) | 1.1 (0.4-3.0) | 1.1 (0.4-3.6) | 1.0 (0.3-3.6) |
| Second or Later Birth, aOR (95% CI) | 1.3 (0.4-4.0) | 1.4 (0.3-5.7) | 0.4 (0.1-1.7) |
| **Endometriosis** | **N=46**  | **N=35**  |  **N=39** |
| Total sample, Unadjusted OR (95% CI) | 2.1 (1.2-3.8) | 2.4(1.2-4.8) | 2.2 (1.2-4.3) |
| Total Sample, aOR (95% CI) | 2.5 (1.3-4.7)  | 3.2 (1.5-6.8)  | 2.7 (1.3-5.5)  |
| First Birth, aOR (95% CI) | 1.8 (0.8-4.7) | 3.0 (0.998-8.5) | 2.3 (0.7-6.7) |
| Second or Later Birth, aOR (95% CI) | 3.3 (1.3-8.3) | 3.7 (1.3-10.8) | 3.3 (1.3-8.5) |
| **Uterine Problem** |  **N=48** |  **N=38** | **N=42**  |
| Total sample, Unadjusted OR (95% CI) | 2.5 (1.4-5.0) | 2.5 (1.3-4.8) | 2.8 (1.5-5.3) |
| Total Sample, aOR (95% CI) | 2.4 (1.3-4.5)  |  2.1 (1.0-4.3) | 2.6 (1.3-5.3)  |
| First Birth, aOR (95% CI) | 1.3 (0.6-3.1) | 1.4 (0.5-3.6) | 1.7 (0.7-4.4) |
| Second or Later Birth, aOR (95% CI) | 6.3 (2.2-18.5) | 4.6 (1.5-14.2) | 5.7 (1.9-17.4) |
| **Uterine problem or related problem or diagnosis reported8**  | **N=62**  |  **N=50** |  **N=55** |
| Total sample, Unadjusted OR (95% CI) | 2.5 (1.5-4.3) | 2.4 (1.4-4.3) | 2.8 (1.6-4.8) |
| Total Sample, aOR (95% CI) |  2.6 (1.5-4.5) | 2.3 (1.2-4.2)  |  2.7 (1.5-5.0) |
| First Birth, aOR (95% CI) | 1.6 (0.7-3.4) | 1.7 (0.7-4.0) | 2.0 (0.9-4.5) |
| Second or Later Birth, aOR (95% CI) | 5.3 (2.2-12.9) | 4.0 (1.5-10.4) | 4.9 (1.9-12.4) |
| **Unexplained infertility** |  **N=22** |  **N=20** | **N=19**  |
| Total sample, Unadjusted OR (95% CI) | 1.5 (0.6-3.4) | 1.3 (0.5-3.1) | 1.7 (0.7-4.2) |
| Total Sample, aOR (95% CI) | 1.5 (0.6-3.8)  | 1.3 (0.5-3.3)  |  1.7 (0.6-4.6) |
| First Birth, aOR (95% CI) | 3.3 (0.6-18.6) | 2.0 (0.4-11.1) | 3.9(0.4-35.1) |
| Second or Later Birth, aOR (95% CI) | 1.0 (0.3-3.2) | 0.9 (0.2-3.2) | 1.2 (0.3-4.1) |
| **Male factor infertility** | **N=74**  |  **N=57** | **N=63**  |
| Total sample, Unadjusted OR (95% CI) | 1.2 (0.8-2.0) | 1.5 (0.9-2.6) | 1.2 (0.7-2.0) |
| Total Sample, aOR (95% CI) | 1.1 (0.7-1.9) | 1.5 (0.8-2.7) | 1.1 (0.7-2.0) |
| First Birth, aOR (95% CI) | 1.1 (0.6-2.1) | 1.7 (0.7-3.8) | 1.0 (0.5-2.2) |
| Second or Later Birth, aOR (95% CI) | 1.1 (0.5-2.4) | 1.3 (0.6-3.1) | 1.2 (0.5-2.8) |

1 Specific infertility disorders not mutually exclusive. Data not presented for “more than one maternal infertility disorder” because of questionable model fit due to limited dispersion of confounding variables.

2 Same data as presented in Table 2 presented here for ease of comparison.

3 10 cases and 9 controls with a report of maternal infertility are not further classified within one of the specific types listed on the table because data were missing for the specific type or the verbatim description did not contain sufficient information to allow for classification into one of the maternal infertility disorder types.

4 aOR: odds ratio for total sample adjusted for maternal age at birth, maternal education at birth, maternal race-ethnicity, child sex, and parity; odds ratios for first birth and second or later birth adjusted for the same factors with the exception of parity.

5 PCOS – polycystic ovarian syndrome

6 PCOS/multiple ovarian cysts or related symptoms includes PCOS/multiple ovarian cysts diagnoses + cases without a clear diagnosis mentioned, but healthcare provider noted symptoms consistent with PCOS were related to infertility problems (e.g. overweight associated with ovulation problems).

7 Diminished ovarian reserve includes premature ovarian failure and infertility related to age, chronic disease, or eating disorder.

8 Uterine problem or related problem or diagnosis includes uterine problem diagnoses (such as fibroids) + infertility related to maternal diethylstilbestrol (DES) exposure, infertility secondary to chromosomal defect, infertility associated with cervical issues, and infertility related to problems with progesterone.

Supplemental Table 2. Associations between autism spectrum disorder and maternal or paternal infertility disorders among second births restricted to various subgroups based on prior sibling ASD1 diagnosis and inter-pregnancy interval, Study to Explore Early Development.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Infertility Disorder2** | **Total Second or Later Births3****aOR4 (95% CI)** | **Restricted to No Older Sibling has ASD1 diagnosis** | **Restricted to Inter-pregnancy Interval 18-59 months** | **Restricted to Inter-Pregnancy Interval 60+ months** |
| Any maternal infertility disorder5 | 1.9 (1.3-2.9) | 2.0 (1.02-4.0) | 1.9 (0.9-3.7) | 1.2 (0.5-3.0) |
| Blocked or damaged tubes | 3.4 (1.3-9.3) | 7.2 (1.5-34.1) | 1.6 (0.3-10.7) | 1.2 (0.3-5.1) |
| PCOS1/multiple ovarian cysts | 2.7 (1.2-6.1) | 2.7 (0.9-8.4) | 1.3 (0.3-5.8) | 4.8 (0.5-49.5) |
| PCOS/multiple ovarian cysts or related symptoms reported6 | 2.0 (1.1-3.8) | 2.3 (0.9-5.9) | 0.9 (0.3-2.7) | 9.3 (1.0-86.6) |
| Diminished ovarian reserve7 | 1.3 (0.4-4.0) | 0.5 (0.1-2.7) | 1.3 (0.2-8.1) | 0.7 (0.1-4.9) |
| Endometriosis | 3.3 (1.3-8.3) | 4.7 (0.9-24.8) | 1.7 (0.4-7.4) | 3.4 (0.3-40.1) |
| Uterine problem *(e.g. fibroids)* | 6.3 (2.2-18.5) | -9 | 6.5 (1.5-28.3) | 8.2 (0.9-76.3) |
| Uterine problem or related problem or diagnosis reported8 | 5.3 (2.2-12.9) | 26.7 (2.7-264.3) | 7.6 (1.8-31.4) | 4.5 (0.8-26.6) |
| Unexplained infertility | 1.0 (0.3-3.2) | 0.3 (0.03-3.9) | 1.1 (0.1-10.4) | -9 |
| Male factor infertility | 1.1 (0.5-2.4) | 0.9 (0.2-3.9) | 2.3 (0.5-11.1) | 0.5 (0.1-2.3) |

1ASD – autism spectrum disorder case group; PCOS – polycystic ovarian syndrome

2 Specific infertility disorders not mutually exclusive. Data not presented for “more than one maternal infertility disorder” because of questionable model fit due to limited dispersion of confounding variables.

3 Same data as presented in Table 2 presented here for ease of comparison.

4 aOR: odds ratio adjusted for maternal age at birth, maternal education at birth, maternal race-ethnicity, and child sex.

5 10 cases and 9 controls with a report of maternal infertility are not further classified within one of the specific types listed on the table because data were missing for the specific type or the verbatim description did not contain sufficient information to allow for classification into one of the maternal infertility disorder types.

6 PCOS/multiple ovarian cysts or related symptoms includes PCOS/multiple ovarian cysts diagnoses + cases without a clear diagnosis mentioned, but healthcare provider noted symptoms consistent with PCOS were related to infertility problems (e.g. overweight associated with ovulation problems).

7 Diminished ovarian reserve includes premature ovarian failure and infertility related to age, chronic disease, or eating disorder.

8 Uterine problem or related problem or diagnosis includes uterine problem diagnoses (such as fibroids) + infertility related to maternal diethylstilbestrol (DES) exposure, infertility secondary to chromosomal defect, infertility associated with cervical issues, and infertility related to problems with progesterone.

9 Model failed to converge.

**Supplemental Table 3. Distribution of disorders and treatments among mothers reporting an infertility disorder only, infertility treatment only, or both, Study to Explore Early Development.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Infertility disorder, NO treatment** | **Infertility disorder, NO treatment** | **Infertility disorder and treatment** |
|  | **ASD (n=64)** | **POP (N=65)** | **ASD (N=61)** | **POP (N=79)** | **ASD (N=60)** | **POP (N=73)** |
|   | **N** | % | **N** | % | **N** | % | **N** | % | **N** | % | **N** | % |
| **Infertility Disorders** |  |  |  |  |  |  |  |  |  |  |  |  |
| Any maternal infertility disorder | 64 | 100.0 | 65 | 100.0 | 0 | 0.0 | 0 | 0.0 | 60 | 100.0 | 73 | 100.0 |
| Blocked or damaged tubes | 10 | 15.6 | 3 | 4.6 | 0 | 0.0 | 0 | 0.0 | 10 | 16.7 | 10 | 13.7 |
| PCOS/multiple ovarian cysts | 13 | 20.3 | 21 | 32.3 | 0 | 0.0 | 0 | 0.0 | 20 | 33.3 | 25 | 34.2 |
| PCOS/multiple ovarian cysts or related symptoms reported | 21 | 32.8 | 34 | 52.3 | 0 | 0.0 | 0 | 0.0 | 26 | 43.3 | 37 | 50.7 |
| Diminished ovarian reserve | 5 | 7.8 | 9 | 13.8 | 0 | 0.0 | 0 | 0.0 | 11 | 18.3 | 9 | 12.3 |
| Endometriosis | 10 | 15.6 | 7 | 10.8 | 0 | 0.0 | 0 | 0.0 | 17 | 28.3 | 12 | 16.4 |
| Uterine problem (e.g. fibroids) | 20 | 31.3 | 8 | 12.3 | 0 | 0.0 | 0 | 0.0 | 10 | 16.7 | 10 | 13.7 |
| Uterine problem or related problem or diagnosis reported | 25 | 39.1 | 11 | 16.9 | 0 | 0.0 | 0 | 0.0 | 14 | 23.3 | 12 | 16.4 |
| Unexplained infertility | 3 | 4.7 | 4 | 6.2 | 0 | 0.0 | 0 | 0.0 | 8 | 13.3 | 7 | 9.6 |
| **Infertility Treatments** |   |   |   |   |   |   |   |   |   |   |   |   |
| Any maternal infertility treatment | 0 | 0.0 | 0 | 0.0 | 61 | 100.0 | 79 | 100.0 | 60 | 100.0 | 73 | 100.0 |
| Any maternal surgery for infertility condition | 0 | 0.0 | 0 | 0.0 | 12 | 19.7 | 21 | 26.6 | 22 | 36.7 | 28 | 38.4 |
| Any medication for miscarriage or infertility | 0 | 0.0 | 0 | 0.0 | 56 | 91.8 | 70 | 88.6 | 52 | 86.7 | 61 | 83.6 |
| Ovarian stimulation – anti estrogens | 0 | 0.0 | 0 | 0.0 | 12 | 19.7 | 21 | 26.6 | 22 | 36.7 | 28 | 38.4 |
| Ovarian stimulation – gonadotropins | 0 | 0.0 | 0 | 0.0 | 14 | 23.0 | 14 | 17.7 | 16 | 26.7 | 19 | 26.0 |
| Progesterone | 0 | 0.0 | 0 | 0.0 | 34 | 55.7 | 40 | 50.6 | 32 | 53.3 | 42 | 57.5 |
| HCG and related | 0 | 0.0 | 0 | 0.0 | 12 | 19.7 | 12 | 15.2 | 14 | 23.3 | 18 | 24.7 |
| Gonadotropin agonist/antagonist | 0 | 0.0 | 0 | 0.0 | 10 | 16.4 | 8 | 10.1 | 9 | 15.0 | 10 | 13.7 |
| Other hormonal meds such as estrogen | 0 | 0.0 | 0 | 0.0 | 7 | 11.5 | 6 | 7.6 | 1 | 1.7 | 5 | 6.8 |
| Other meds to prevent miscarriage (anti -coagulants, anti-inflammatory, etc) | 0 | 0.0 | 0 | 0.0 | 15 | 24.6 | 14 | 17.7 | 10 | 16.7 | 16 | 21.9 |
| Assisted reproductive technology | 0 | 0.0 | 0 | 0.0 | 13 | 21.3 | 13 | 16.5 | 13 | 21.7 | 17 | 23.3 |
| Assisted insemination | 0 | 0.0 | 0 | 0.0 | 6 | 9.8 | 13 | 16.5 | 11 | 18.3 | 12 | 16.4 |