## Supplementary Table 5. Safety: incidence of OHSS, ectopic pregnancy, and complications during pregnancy and delivery.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Study Groups** | **Event Rate n/N (%), Odds Ratio (95%CI), and p-value** | | | | | | | | | |
| **OHSS** | **Ectopic pregnancy** | **Gestational diabetes** | **PIH or preeclampsia** | **Placenta praevia** | **Placental abruption** | **Preterm delivery/birth** | **Early preterm delivery/birth** | **Caesarean section delivery** | **Other** |
| **Maternal age** | | | | | | | | | | | |
| Frangez et al. (2014)  *Add. primary study* | Number of studies |  |  |  |  |  |  | 1 |  |  |  |
| Age <33 (ref.) |  |  |  |  |  |  | nr |  |  |  |
| Age ≥33 |  |  |  |  |  |  | nr |  |  |  |
| Age <36 (ref.) |  |  |  |  |  |  | nr |  |  |  |
| Age ≥36 |  |  |  |  |  |  | nr |  |  |  |
| OR (95% CI)  p-value |  |  |  |  |  |  | 1.03 (0.68, 1.56)  p=0.877  1.25 (0.69, 2.24)  p=0.451 |  |  |  |
| Kort et al. (2012)  *Add. primary study* | Age ≤42 (ref.) |  |  | nr (2.8%) | nr (11.4%) | nr (0%) | nr (14.3%) |  |  | nr (nr) |  |
| Age ≥50 |  |  | nr (2.0%) | nr (7.9%) | nr (1.0%) | nr (8.9%) |  |  | nr (86%) |  |
| OR (95% CI)  p-value |  |  | 0.70 (0.06,7.96)  nr | 0.67 (0.19,2.40)  nr | nr  nr | 0.59 (0.18,1.89)  nr |  |  | nr  not sig. |  |
| • SGA: singleton pregnancy | Age ≤42 (ref.) |  |  | nr (0%) | nr (0%) | nr (0%) | nr (10.0%) |  |  |  |  |
| Age ≥50 |  |  | nr (2.7%) | nr (5.4%) | nr (5.4%) | nr (4.1%) |  |  |  |  |
| OR (95% CI)  p-value |  |  | nr  nr | nr  nr | nr  nr | 0.38 (0.06,2.5)  nr |  |  |  |  |
| **Maternal weight/BMI** | | | | | | | | | | | |
| Koning et al. (2012)  *Meta-analysis* | Number of studies | 4 | 5 |  |  |  |  |  |  |  |  |
| BMI ≤25 (ref.) | 149/1975 (7.5%) | 50/1660 (3.0%) |  |  |  |  |  |  |  |  |
| BMI >25 | 109/1469 (7.4%) | 21/760 (2.8%) |  |  |  |  |  |  |  |  |
| OR (95% CI)  p-value | 1.00 (0.77,1.29)  0.99 | 0.96 (0.54, 1.70)  0.89 |  |  |  |  |  |  |  |  |
| Maheshwari et al. (2007)  *Meta-analysis* | Number of studies | 4 |  |  |  |  |  |  |  |  |  |
| BMI <25 (ref.) | 50/916 (5.5%) |  |  |  |  |  |  |  |  |  |
| BMI ≥25 | 53/868 (6.1%) |  |  |  |  |  |  |  |  |  |
| OR (95% CI)  p-value | 1.12 (0.74,1.68)  0.60 |  |  |  |  |  |  |  |  |  |
| Number of studies | 4 |  |  |  |  |  |  |  |  |  |
| BMI <30 (ref.) | 68/1363 (5.0%) |  |  |  |  |  |  |  |  |  |
| BMI ≥30 | 20/369 (5.4%) |  |  |  |  |  |  |  |  |  |
| OR (95% CI)  p-value | 1.16 (0.69, 1.96)  0.58 |  |  |  |  |  |  |  |  |  |
| Frangez et al. (2014)  *Add. primary study* | Number of studies |  |  |  |  |  |  | 1 |  |  |  |
| BMI <18 |  |  |  |  |  |  | nr |  |  |  |
| BMI 18-30 (ref.) |  |  |  |  |  |  | nr |  |  |  |
| BMI >30 |  |  |  |  |  |  | nr |  |  |  |
| OR (95% CI)  p-value |  |  |  |  |  |  | 1.97 (0.84, 4.62)  p=0.120  1.86 (1.06, 3.27)  p=0.031 |  |  |  |
| Dickey et al. (2013)  *Add. primary study*  • singletons | Number of studies |  |  |  |  |  |  | 1 | 1 |  | 1\* |
| BMI 12.0-18.4 |  |  |  |  |  |  | nr | nr |  | nr |
| BMI 18.5-24.9 (ref.) |  |  |  |  |  |  | nr | nr |  | nr |
| BMI 25.0-29.9 |  |  |  |  |  |  | nr | nr |  | nr |
| BMI 30.0-34.9 |  |  |  |  |  |  | nr | nr |  | nr |
| BMI ≥35 |  |  |  |  |  |  | nr (16.4%) | nr (3.6%) |  | nr (1.7%) |
| OR (95% CI)  p-value |  |  |  |  |  |  | 1.1 (1.0, 1.3)†  1.2 (1.2, 1.3)†  1.4 (1.3, 1.5)†  1.5 (1.4, 1.6)†  †p<0.01 | 0.9 (0.6, 1.5)‡  1.5 (1.3, 1.8)†  1.9 (1.6, 2.3)†  2.2 (1.8, 2.8)†  ‡not sig., †p<0.01 |  | 0.6 (0.2, 1.5)‡  1.6 (1.2, 2.1)†  2.1 (1.6, 2.9)†  2.6 (1.8, 3.6)†  ‡not sig., †p<0.01 |
| • twins | Number of studies |  |  |  |  |  |  | 1 | 1 |  | 1\* |
| BMI 12.0-18.4 |  |  |  |  |  |  | nr | nr |  | nr |
| BMI 18.5-24.9 (ref.) |  |  |  |  |  |  | nr | nr |  | nr |
| BMI 25.0-29.9 |  |  |  |  |  |  | nr | nr |  | nr |
| BMI 30.0-34.9 |  |  |  |  |  |  | nr | nr |  | nr |
| BMI ≥35 |  |  |  |  |  |  | nr (63.4%) | nr (12.5%) |  | nr (6.5%) |
| OR (95% CI)  p-value |  |  |  |  |  |  | 1.0 (1.0, 1.2)‡  1.0 (0.9, 1.0)‡  1.1 (1.0, 1.1)‡  1.1 (1.0, 1.1)‡  ‡not sig. | 1.3 (1.0, 1.6)‡  1.2 (1.1, 1.4)†  1.3 (1.1, 1.5)†  1.5 (1.3, 1.8)†  ‡not sig., †p<0.01 |  | 0.9 (0.5, 1.5)‡  1.4 (1.2, 1.8)†  1.5 (1.2, 1.9)†  2.4 (1.8, 3.0)†  ‡not sig., †p<0.01 |
| Dickey et al. (2012)  *Add. primary study*  • singletons | Number of studies |  |  |  |  |  |  | 1 | 1 |  | 1\* |
| BMI 18.4-24.9 (ref.) |  |  |  |  |  |  | 723 (5.4%) | 166 (1.2%) |  | 69 (0.5%) |
| BMI 25.0-29.9 |  |  |  |  |  |  | 345 (7.1%) | 89 (1.8%) |  | 38 (0.8%) |
| BMI 30.0-34.9 |  |  |  |  |  |  | 171 (8.4%) | 48 (2.4%) |  | 23 (1.1%) |
| BMI ≥35 |  |  |  |  |  |  | 134 (9.7%) | 39 (2.8%) |  | 13 (0.9%) |
| OR (95% CI)  p-value |  |  |  |  |  |  | 1.34 (1.17,1.53), 1.61 (1.35,1.92), 1.87 (1.54,2.28), <0.01 | 1.47 (1.13,1.91), 1.91 (1.38,2.64), 2.27 (1.59,3.23)  <0.01 |  | 1.52 (1.02,2.27)‡, 2.20 (1.36,3.54)†, 1.82 (1.01,3.31)‡  ‡<0.05, †<0.01 |
| • twins | Number of studies |  |  |  |  |  |  | 1 | 1 |  | 1\* |
| BMI 18.4-24.9 (ref.) |  |  |  |  |  |  | 1976 (35.1%) | 333 (5.9%) |  | 112 (2.0%) |
| BMI 25.0-29.9 |  |  |  |  |  |  | 937 (36.3%) | 182 (7.1%) |  | 83 (3.2%) |
| BMI 30.0-34.9 |  |  |  |  |  |  | 374 (37.5%) | 82 (8.0%) |  | 37 (3.6%) |
| BMI ≥35 |  |  |  |  |  |  | 244 (42.4%) | 66 (11.5%) |  | 35 (6.1%) |
| OR (95% CI)  p-value |  |  |  |  |  |  | 1.07 (0.97,1.18)‡, 1.09 (0.95,1.25)‡, 1.36 (1.14,1.62)†  ‡not sig., †<0.01 | 1.21 (1.01,1.46)‡, 1.39 (1.08,1.79)†, 2.02 (1.52,2.68)†  ‡<0.05, †<0.01 |  | 1.62 (1.21,2.16), 1.84 (1.26,2.69), 3.15 (2.13,4.66)  <0.01 |
| Zander-Fox et al. (2012)  *Add. primary study* | Number of studies |  |  | 1 | 1 |  |  | 1 (singleton) |  | 1 |  |
| BMI 18.5-24.9 (ref.) |  |  | nr (5.1%) | nr (12.8%) |  |  | 26 (8.8%) |  | 115 (36.1%) |  |
| BMI 25.0-29.9 |  |  | nr | Nr |  |  | 17 (12.4%) |  | 63 (42.6%) |  |
| BMI 30.0-34.9 |  |  | nr | nr |  |  | 10 (13.9%) |  | 38 (50.7%)† |  |
| BMI 35-39.9 |  |  | nr (55.6%) | nr (44.4%) |  |  | 7 (16.3%) |  | 20 (44.4%) |  |
| BMI ≥40 |  |  | nr | nr |  |  | 4 (16.0%) |  | 12 (42.9%) |  |
| OR (95% CI)  p-value |  |  | nr  <0.05 | nr  <0.05 |  |  | nr  not sig. |  | nr  †<0.01 |  |
| **Maternal smoking** | | | | | | | | | | | |
| Waylen et al. (2009)  *Meta-analysis* | Number of studies |  | 3 |  |  |  |  |  |  |  |  |
| Non-smokers (ref.) |  | nr |  |  |  |  |  |  |  |  |
| Smokers |  | nr |  |  |  |  |  |  |  |  |
| OR (95% CI)  p-value |  | 15.69 (2.87, 85.76)  nr |  |  |  |  |  |  |  |  |
| • SGA: studies where age not likely to be a confounder | Number of studies |  | 2 |  |  |  |  |  |  |  |  |
| Non-smokers (ref.) |  | nr |  |  |  |  |  |  |  |  |
| Smokers |  | nr |  |  |  |  |  |  |  |  |
| OR (95% CI)  p-value |  | 14.70 (1.53, 141.15)  nr |  |  |  |  |  |  |  |  |
| \*Very early preterm birth (<28 weeks gestation)  Definitions:  • Ectopic pregnancy: diagnosed in most studies by ultrasound visualization of gestational sac in fallopian tube; ectopic pregnancy rates reported per pregnancy in Waylen et al. (2009), and per woman/couple in Koning et al. (2010)  • Gestational diabetes = high blood sugar diagnosed during pregnancy  • Pregnancy-induced hypertension (PIH) = high blood pressure during pregnancy  • Preeclampsia = development of high blood pressure and protein in the urine during the 2nd-3rd trimesters of pregnancy  • Placenta praevia = implantation of the placenta over or near the cervix during the 2nd-3rd trimesters of pregnancy  • Gestation: term birth/delivery = birth/delivery at >37 weeks; preterm birth/delivery (PTB or PTD) = birth or delivery at <37 weeks gestation; moderate preterm birth/delivery = birth or delivery at <34 weeks gestation; early or very preterm birth/delivery = birth or delivery at <32 weeks gestation | | | | | | | | | | | |