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| **TABLE 2: OVERVIEW OF THE STUDIES INCLUDED IN THE REVIEW** |  |  |  |  |  |
| **AUTHORS** | **No. Cases** | **INCLUSION**  | **OVERALL** | **NTD** | **CHD** | **OROFACIAL** | **MSK** | **OTHERS** | **COMMENT** |
| **REVIEW & METANALYSIS** |  |  |  |  |  |  |  |  |
| Stothard et al | 18 studies |  | Heterogenicity of OR 0.0 - 62.9% | 1.87 (1.62-2.15) Affect size greater for Spina Bifida than Anencephaly | 1.3 (1.12-1.51) Septal anomaly more common than other | septal 1.2 (1.09-1.31); CP 1.23 (1.03-1.47); CL + CP 1.2 (1.03-1.40) | limb reduction 1.34 (1.03-1.73) | Hydrocephalus 1.68 (1.19-2.36) |  |
| Leddy et al |  |  |  **NTD:** 1.8 (1.1-3.0), Spina bifida 2.6(1.5-4.5) | 1.2(1.1-1.3) |  |  | Omphalo 3.3 (1.0-10.3) |  |
| **PROSPECTIVE/COHORT STUDY** |  |  |  |  |  |  |  |
| Moore et al | 22,951 preg | Amnio, AFP, anomalies, deaths or fetal loss | None for BMI >28, (PR 0.95; CI = 0.62-1.5)  | None | None except septal defects | -PR 2.2 (95% CI 0.91–5.4 | PR 1.5 (95% CI 5 0.69 –3.4) | club foot | Obesity + Diabetes - PR 3.1(95% CI 1.2-7.6) |
| Rankin et al | 41013 | miscarriage (> 20 weeks), TOPFA, live & still births | CVS ,urinary, nervous, digestive, orofacial | 1.85 (0.66-5.21) | 1.16 (0.84-1.59), VSD 1.56 (1.01-2.40) | 1.76(0.84-3.66), cleft lip 3.71 (1.05-13.10) | 1.77(0.16-19.98 | Eye 11.36(2.25-57.28) |  |
| Feldman et al | 72,915 consecutive cases |  | Differences in weights ranges not statistically significant (÷2 = 5.997, p = 0.19, power = 0.99). Obese and non-obese difference statistically not significant |
| Mandal et al. | 422 cases,422 controls |  | 5 (1.2%) congenitally malformed.  |  |  |  |  |  |  |
| Owens et al  | 2,329 women |  | 37 (1.6%) ; OR 2.47 (1.09–5.60, *P* = 0.03) |  |  |  |  |  |  |
| Villamor et al | 220,328 |  |  | **OROFACIAL:** Adjusted odds - isolated CP & all CP > 2.3 times for 3 BMI units gain between pregnancies, visa vis BMI change −1 to <1 units | **COMMENT** 3 BMI units ~ 8 kg (17.6 pounds) for ave. height (1.65 m) woman who weighed 63 kg at the first pregnancy |
| **RETROSPECTIVE / CASE CONTROL STUDY** |  |  |  |  |  |  |
| Shaw et al  | 1052343 +additional 208387 for clefts | live and still births, TOPFA | +ve assoc. with overall NTD - 95% CI 0.26-0.79. No significant assoc. with other anomalies | **COMMENT**: Multivitamin & Diabetes didn't significantly alter findings |
| Mills et al | 1536828 | live births |   |  | **CHD**: > 30 OR 1.15 (1.07-1.23); > 40 OR 1.33 (1.15-1.54)  |  |  |
| Anderson et a | cases 477 controls 497 |  | **NTD:** Anencephaly OR 2.3 CI (1.2-4.3), Spina Bifida OR 2.8 CI (1.7-4.5), hydrocephaly OR 2.7 CI (1.5-5.0) |  | **COMMENT:** OR is higher with simultaneous diabetes showing multiplicative interaction |
| Watkins et al |  | Deliveries with/without birth defects |  | Spina bifida OR 3.5 CI (1.2-10.3) | OR 2.0 CI (1.2-3.4) |  |  | Omphalocele OR 3.3 CI (1.0-10.3) |
| Cedergen MI, Kallen BA | 812457 | All deliveries |  |  | **CHD:** OR 1.18 CI (1.09-1.27), for severe CHD OR 1.23 CI (1.05-1.44); For morbid Obesity OR 1.40 CI (1.22-1.64) & for severe CHD OR 1.69 CI (1.27-2.26)Only ASD and VSD are significant |
| Watkins ML, Botto LD | 1049 cases vs 3029 control | Deliveries |  |  | Overweight & Obese OR 1.36 CI (0.95-1.93).  |  |  | **COMMENT:** multivitamin didn't reduce of anomalies among overweight and Obese |
| Hendricks et al | 149 cases & 178 controls | OR 1.73 CI (1.03-2.92 |  | **COMMENT:** Hyperinsulinemia independent risk for NTD-OR 1.91 CI (1.21-3.01)  |
| Honein et al | 169 cases & 2763 controls | Deliveries | Only assoc. with joint exposure to subfertility & high BMI |  | **Renal anomalies** OR 5.8 CI (2.0-16.3). Obstructive anom. OR 8.5 CI (2.9-24.7). | No assoc. for single exposure |
| McMahon et al | 179 cases & 288 controls | Deliveries and TOPFA  |   | OR 2.06 CI (1.12-3.81) |  |  |  |   |  |
| Waller et al | on-going | Deliveries | Adjusted after exclusion of diabetes | Spina bifida: OR 2.09; 95% CI, 1.63-2.70 | OR, 1.26; 95% CI 1.11-1.43 |  | limb red. OR, 1.16; CI, 0.89-1.52 | omphalo: OR 1.27; 95% CI, 0.83-1.96) |  |
| Cedergen MI, Kallen BA | 1686 cases and 988,171 controls | live and still births |  |  |  | **OROFACIAL CLEFTS** 1686 cases @ 1.7/1000 births. CP occurred in 36%, CL in 25%, and CLP in 38% | **COMMENT** 1408 (84%) of the orofacial clefts were isolated (i.e., the cleft was the only major congenital malformation present). |
| Best et al  | 132885 pregnancies | late miscarriage, TOPFA, Live/ still births | Antenatal anomaly detection 59.7%, 52.6%, 48.1% and 45.8% in under-wt, normal BMI, overweight and obese, respectively | **COMMENT** 67 (4.0%) anomalies occurred in underweight, 793(47.0%) in recommended BMI, 468(27.8%) in overweight and 358 (21.2%) in obese. |
| Ray et al. | 420,362 women | Live/Still births, MTPs, USG, fetal autopsies  | **NTDs** : 292 open NTDs Q2: 57.1–64.1 (101,513) aOR 2.1 (1.4–3.2). Adjusted odds ratio (OR) for NTD 1.2 (95% [CI] 1.1-1.3) per 10-kg incremental rise in maternal weight. |  |  | **COMMENT** For the highest compared with lowest weight deciles (adjusted OR 3.3, 95% CI 1.7-6.2) |