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REVIEW ARTICLE

Journal Watch

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Metformin versus placebo in obese pregnant women without diabetes mellitus. Syngelaki A, Nicolaides KH, Balani J, Hyer S, Akolekar R, Kotecha R, et al. N Engl J Med. 2016 Feb 4;374(5):434-43. doi: 10.1056/NEJMoa1509819.

Obesity is now well-known causing issue in terms of short- and long-term sequelae to both mothers and babies. Interventions on diet and/or lifestyle have not been successful in reducing obesity-related complications in pregnancy.

Obesity is associated to hyperglycemia and insulin resistance, causing macrosomia and additional pregnancy complications. Many studies on gestational diabetic pregnancies have shown that metformin suppresses insulin resistance and reduces gestational weight gain. On this ground, the metformin in obese (BMI greater than 35) nondiabetic pregnant women trial aimed to demonstrate the effect of this drug treatment in reducing the median neonatal birth weight (MNBW) z-score. Previous publications show that with BMI > 35, the MNBW z-score is 0.3 SD higher than cases with BMI < 35. Therefore, the study hypothesis was that metformin in women with BMI > 35 reduces the MNBW z-score by at least 0.3 SD. The inclusion criteria of this double-blind, placebo-controlled study were: singleton pregnancy, BMI > 35, and 12–18 weeks' gestational age at recruitment. Women were recruited in three NHS hospitals in the UK. The study excluded maternal age under 18 years, presence of a major fetal defect on the first trimester scan, history of GDM, kidney, liver, or heart failure, any other serious medical condition, hyperemesis gravidarum, women already on metformin, or with known sensitivity to it. Women fulfilling these criteria were randomly assigned either to the placebo or to the metformin treatment group, in a 1:1 ratio. The initial dose was 1.0 g QD, gradually increased up until 3.0 g QD (or up to the maximum tolerated dose) in five weeks. The regimen was stopped, if there was evidence of FGR. Insulin was added to the metformin treatment, when necessary. The primary outcome was the median neonatal birth weight z-score. A series of maternal and fetal secondary outcomes were also analyzed. Four hundred women were finally included in the study, 202 in the metformin, and 198 in the placebo group.

No significant difference was observed in the MNBW z-score—metformin group median: 0.05 (IQR: −0.71 to 0.92), placebo group median: 0.17 (IQR: −0.62 to 0.89), $p = 0.66$). No difference was seen in the incidence of LGA or adverse fetal/neonatal outcome. The median gestational weight gain was lower in the metformin group [median 4.6 kg (IQR: 1.3–7.2)] than in the placebo group [6.3 kg (IQR: 2.9–9.2)], $p < 0.001$. The incidence of pre-eclampsia was significantly reduced (3 vs. 11.3 %—OR: 0.24, 95 % CI: 0.10–0.61). Other secondary outcomes and incidence of serious adverse events were no different between the groups. The major strength compared to other similar studies is the racial heterogeneity, making it applicable to the general population. In conclusion, the administration of metformin in obese nondiabetic pregnant women did not reduce either the MNBW z-score or the LGA incidence. However, it leads to lower incidence of pre-eclampsia and a modest reduction of gestational weight gain.

True risk of fetal/neonatal alloimmune thrombocytopenia in subsequent pregnancies: a prospective

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observational follow-up study. Tiller H, Husebekk A, Skogen B, Kjeldsen-Kragh J, Kjaer M. BJOG. 2016 Apr;123(5):738-44. doi: 10.1111/1471-0528.

Fetal/Neonatal alloimmune thrombocytopenia (FNAIT) is due to human platelet antigen (HPA) fetomaternal incompatibility. In the majority of cases, anti-HPA-1a antibodies are responsible. The most serious complication is intracranial hemorrhage (ICH). The recurrence risk of the related fetal ICH has been previously studied. However, there are few reports on the natural history of FNAIT in subsequent pregnancies, which was the aim of this study.

This is a prospective observational study, recruiting immunized woman from the Norwegian screening and intervention study. In the latter, pregnant women with anti-HPA-1a antibodies were offered earlier C-section delivery and immediate platelet (PLT) transfusion at birth were required, without any prenatal treatment. Fifty women of the Norwegian screening study (index pregnancies) were identified and there were 62 subsequent pregnancies. HPA-1a compatible pregnancies and pregnancies in which HPA incompatibility could not be confirmed were excluded, leaving 45 subsequent pregnancies. Anti-HPA1a antibodies were checked at 22 and 34 weeks' gestation, and six weeks after birth. Women were considered at high risk if the level was >3 IU/mL. They were delivered two weeks before term, and immediate transfusion was offered if the babies showed bleeding signs or newborn PLT count was $<35 \times 10^6$/L. The risk of ICH correlates with the PLT count. Therefore, newborn PLT count was used as a surrogate outcome.

The rate of preterm delivery (36 and 36 %) and C-section (82 and 88 %) were comparable in index and subsequent pregnancies, respectively. No cases of ICH were seen in the subsequent pregnancies, compared to one case in the index pregnancy. FNAIT developed in 9/50 (38 %) index neonates, compared to 13/45 (29 %) subsequent neonates. Neither the unadjusted nor adjusted PLT count showed significant differences in the two groups. A linear mixed model analysis was used to assess the impact of parity. This showed an estimated PLT count increase of 26×10^9/L per birth. To assess the individual PLT pattern variation in sequential newborns of each woman, the PLT counts were categorized as severe thrombocytopenia ($1–49 \times 10^9$/L), moderate thrombocytopenia ($50–149 \times 10^9$/L) or normal ($>150 \times 10^9$/L). Comparing the index neonates with the first subsequent neonates, 18 % of the first subsequent pregnancies were in the category with higher PLT count, 52 % were in the same category, and 30 % had a lower category level. Of those pregnancies with low newborn PLT count in the index pregnancy, 2/3 newborns had unchanged, and 1/3 had a lower PLT count in the subsequent pregnancy. Severe thrombocytopenia in index neonates remained severe in 71 % of subsequent neonates (10/14), and improved to moderate or normal in the remaining four. An increase in the HPA-1a antibody level in the subsequent pregnancy correlated with a recurrence of thrombocytopenia in the subsequent neonates. Similarly, improvement of PLT count was observed when HAP-1a antibody levels were lower.

In conclusion, these data do not support the common opinion that FNAIT and HPA-1a alloimmunization outcomes get worse in the subsequent pregnancies, as two out of three younger siblings of FNAIT-affected children had unchanged or higher PLT count. The correlation between maternal antibody level changes and PLT count patterns may also help in the risk stratification.

Prevalence of a positive TORCH and parvovirus B19 screening in pregnancies complicated by polyhydramnios. Pasquini L, Seravalli V, Sisti G, Battaglini C, Nepi F, Pelagalli R, et al. Prenat Diagn. 2016 Mar;36(3):290-3. doi: 10.1002/pd.4769**. Epub 2016 Feb 8.**

About 1–2 % of pregnancies are complicated by polyhydramnios. The most common cause remains unexplained (up to 50 %), but other possibilities include fetal structural abnormalities, alloimmunization, maternal diabetes, feto-maternal hemorrhage, placental tumors, fetal infections (CMV, toxoplasmosis, syphilis, rubella, parvo B19). Retrospective studies reported the rate of infections varying from 0.3 to 2.9 %.

This retrospective observational study aimed to establish the rate of fetal infection in pregnancies with polyhydramnios, recruited from a tertiary care center, in order to determine whether TORCH and parvovirus B16 testing should be performed if no other obvious cause of polyhydramnios could be identified.

The inclusion criteria were singleton pregnancies with prenatally diagnosed polyhydramnios (AFI >25 or deepest pool >8), >20 weeks gestation, with TORCH, and parvo B19 screening. The polyhydramnios was classified as mild (25–29.9 cm), moderate (30–34.9 cm), and severe (>35 cm). Unknown delivery outcome was an exclusion criterion. Polymerase chain reaction (PCR) on the amniotic fluid was performed in case of positive test for toxoplasma, CMV, and rubella, while the women positive for parvo B19 received the same test only if an amniocentesis was performed. Amongst the 342 patients with polyhydramnios identified, 290 met the inclusion criteria. In 56/290 (19 %) cases, a condition associated with polyhydramnios was diagnosed (diabetes, or gastrointestinal obstructive lesions, isoimmunization, chromosomal abnormalities, or genetic syndromes). Amongst the remaining 234 patients, 49 (20.9 %) had spontaneous resolution at a mean gestational age of 36 weeks. TORCH and parvo B16 resulted positive (two for parvo and one for toxo) in only 1 % (95 %CI: 0–4 %), and the

polyhydramnios persisted until delivery. No evidence of fetal anemia was seen in either of the two cases with positive maternal serology for parvovirus. The PCR on the amniotic fluid of the mother with positive maternal serology for toxoplasma infection was negative. Serum testing did not identify congenital infection in any of the newborns (0 %, 95 %CI: 0–2 %). The authors conclude that the prevalence of maternal infection is very low (1 %) with ultrasound finding of isolated polyhydramnios and should not be an indication for complete infectious disease screening. This would result in a reduction of costs and maternal anxiety.