Selected Summaries

Caffeine and Fetal Growth

[Cook DG, Peacock JL, Feyerabend C, Carey IM, Jarvis MJ, Anderson HR et ah Relation of caffeine intake and blood caffeine concentrations during pregnancy to fetal growth: Prospective population based study. Brit Med J, 1996; 313: 1358-1362].

The authors attempt to find out the effect of caffeine intake during pregnancy upon the fetal growth objectively by measuring plasma caffeine levels. One thousand seven hundred and twenty four white pregnant mothers attending District General Hospital, South London between 1982-1984 were enrolled in a prospective population based study to assess the effect on birth weight of smoking, alcohol, caffeine, socio-economic factors and psycho-social stress(1). Stored plasma was available for 1500 women on atleast one occasion and for 640 women on all three occasions (at bookings, 28 weeks and 36 weeks). Blood levels of caffeine and cotinine (marker for cigarette smoking) were analyzed in the samples by a sensitive gas chromatography technique in 1994.

Study subjects were interviewed on 3 occasions (booking, 28 and 36 weeks) by a structured questionnaire. Caffeine intake was defined by the number of cups of tea, coffee, cocoa and cola drink in the previous week and using the conversion formulae for caffeine (tea = 70 mg/cup, coffee = 92 mg/cup, cocoa = 5 mg/cup and cola = 40 mg/cup). Data from women who had caffeine levels measured on all 3 occasions were only used for analysis (geometric mean blood caffeine concentration). Cotinine levels of 15 mg/ml was taken as the cut off to distinguish smokers from nonsmokers. Out of the 640 women who were thus included in the final analysis, 500 were non-smokers and 140 smokers. Multiple regression analysis was done using a computer software package.

The blood caffeine levels showed an increase of 75% from 2.35 mcg/1 at booking to 4.12 mcg/1 at 36 weeks despite the intake remaining unaltered. Smokers had lower caffeine levels inspite of having a higher intake of caffeine. Caffeine intake showed significant negative correlation with adjusted birth weight (-1.29% g^{-1} $week^{-1}$; p = 0.001) which was no more significant when adjusted for cotinine (-0.06% $g"^{1}$ $week^{-1}$; p = 0.4). Blood caffeine levels showed no relation to adjusted birth weight neither overall nor in cigarette smokers. The authors conclude that birth weight bears no relation to blood caffeine concentrations during pregnancy. They also aver that inadequate control for the confounding effects of cigarette smoking might be the reason for the previously observed negative relation between birth weight and caffeine intake.

Comments

In animal studies caffeine at >80 mg/kg dosage caused fetal loss, decreased fetal weight and size and major skeletal defects(1). Caffeine is readily absorbed from the gut and freely crosses the placenta. It increases the intra cellular cyclic AMP levels and interferes with fetal development. There is evidence that caffeine decreases blood flow in the placental bed by vasoconstriction (2). The FDA in USA advised pregnant women to restrict their intake of

caffeine to <300 mg daily (roughly 3 cups of coffee). In a 1992 review article, 10 out of 13 studies identified a negative influence of caffeine on birth weight. A MEDLINE search yielded 4 subsequent studies and none of them identified caffeine's adverse effect on fetal growth. All these studies were based upon a questionnaire survey for the caffeine intake during pregnancy. Caffeine-cigarette interaction has been described in some studies(3). Smoking accelerates the metabolism of caffeine in the pregnant women and reduces the blood levels inspite of the higher intake generally observed in smokers.

The uniqueness of the present study is that blood caffeine levels were measured and correlated with birth weight after adjusting for confounding variables including cigarette smoking (again objectively by using blood cotinine levels). Cigarette smokers in the present study consumed 50% more caffeine than non smokers. The negative correlation of caffeine intake to birth weight in the overall study group is thus attributed to the confounding effects of cigarette smoking. Caffeine metabolism is slow during pregnancy with a tripling of it's half-life(l). Hence the authors recommended that pregnant women should stop smoking and simultaneously they should drastically cut down their caffeine intake to prevent an overshoot of blood caffeine levels. Previous studies suggest that caffeine intake during first trimester determines the effects on the fetal growth(2). Since the present study uses the mean of three samples taken during pregnancy, there might be a need of larger studies to address this issue.

G. Karthikeyan,
Assistant Professor of Pediatrics,
Government Kasturba Gandhi Hospital
for Women and Children,
Chennai 600 005.

REFERENCES

1. Mokim EM. Caffeine and its effect on pregnancy and the neonate. J Nurse Midwifery 1991; 36:226-231.
2. Fenster L, Eskenazi B, Windham GC, Swan SH. Caffeine consumption during pregnancy and fetal growth. Am J Public Health 1991; 81:458-461.
3. Beaulack-Bailargeon Z. Desrosius C. Caffeine-Cigarette interaction on fetal growth. Am J Obst Gynecol 1987; 157: 1236-1240.

Antenatal use of rhG-CSF

[Calhown DA, Rosa C, Christensen RD. Transplacental passage of recombinant human granulocyte colony-stimulating factor in women with an imminent preterm delivery. Am] Obstet Gynecol 1996; 174:1306-1311].

In this pilot study, authors attempt to find out if recombinant human granulocyte colony stimulating factor (rhG-GSF) administered to mothers with an imminent preterm delivery crosses the placental barrier and exerts biological effect in the neonate. Twenty one mothers with threatened imminent delivery of < 30 weeks gestation were enrolled in the study after excluding those with chorio-amnionitis, abruptio placentae and significant fetal structural abnormality. Eleven mothers received rhG-CSF (25 mcg/kg diluted in 50 ml of 5%

dextrose in water infused intravenously over a 15-30 minute period) whereas 10 mothers served as control subjects. The study being a pilot phase I trial was non randomized, non blinded and non placebo controlled. rhG-CSF concentrations and absolute neutrophil count were measured in maternal and cord blood at the time of delivery. Twelve infants were delivered by the study group mothers and 11 infants by the control group (one mother in each group had a twin pregnancy).

Ten infants were delivered within 30 hours (mean = 10.8 ± 8.9), 8 of them being delivered within 8 h of administration of rhG-CSF (early delivery group). Two infants were delivered after 54 and 108 hours, respectively (late delivery group). In the early delivery group, maternal G-CSF concentrations and blood neutrophil values were significantly higher than in control group including 10 control mothers of present study and 24 historical controls of pregnant women of similar gestation reported in a previous study ($3.1 \times 10^6 + 1.9 \times 10^6$ pg/ml *vs* 27 + 45 pg/ml; $p < 0.05$). Six of the women had elevated absolute neutrophil count (ANC) (27,000 + 11,900 cells/µl *vs* 141400 + 4000 cells/µl; $p < 0.05$). Mothers delivering <2 or >72 h had ANC levels similar to controls. In the early delivery group neonates, 3 out of 10 had cord blood G-CSF concentrations exceeding the control group. Their ANC during the first week of life was, however similar to controls and within the published reference range.

In the late delivery group (n=2), maternal G-CSF concentrations and ANC levels were similar to controls. Their infants had cord blood G-CSF values similar to controls. But their serial ANC levels were persistently above the control range (one infant had ANC 12,000 on D5 and the other had 17,000 on D8, the reference upper limit being 6000 cells/µl).

Two of the 11 women who received rhG-CSF experienced generalized bone pain of 10-25 minutes duration immediately after the infusion. The authors conclude that rhG-CSF crosses the placenta and exerts biological effect upon the fetus, an effect that was most noticeable in mothers receiving rhG-CSF atleast 30 hours before delivery.

Comments

Neonates are handicapped by quantitative and qualitative neutrophil defects like a decreased reserve of stored matured neutrophils and neutrophil progenitors and defects in activation, chemotaxis, phagocytosis and oxidative metabolism(l). The cytokine rhG-CSF accelerates the neutrophil production and upregulates certain neutrophil functions(2). Peripheral neutropenia and depletion of bone marrow storage pool is a hallmark of neonatal sepsis and as many as 50% of preterm infants do suffer from either early onset of infection or nosocomial infection. In the first published report of rhG-CSF use in human neonates, a 654 g neonate at 30 wks gestation with streptococcal sepsis and low ANC was treated with rhG-CSF 910 mcg/kg/day) with resultant increase in ANC and no further septic episodes(3).

In the first randomized placebo controlled trial of rhG-CSF in human neonates, a significant increase in ANC was documented 24 h after 5-10 mcg/kg dosages every 12-24, on days 1,2,3 and was sustained for 96 h. Neutrophil activation and neutrophil storage pool were also increased 24 h after administration. The half life of rhG-CSF is 4.4 + 0.4 hrs(4). It is to be noted that G-CSF has been demonstrated in human milk at concentrations of 45-1551 pg/ml(5).

It is known that vertically acquired neonatal sepsis could undergo such rapid progression that at the time of delivery the infected neonate could be moribund from sepsis. Hence new treatments administered antenatally need evaluation. In a rat model it was observed that a single dose of 50 mcg/kg of rhG-CSF given to pregnant rats one day before delivery resulted in maternal peak G-CSF concentration of 1200 ng/ml and fetal serum peak concentration of 1.5 ng/ml. Though fetal serum levels were 1000 fold lesser than maternal serum levels, rhG-CSF induced a myeloid hyperplasia in the newborn marrow and a 2-4 fold increase in ANC(6).

The present study being a phase I trial raises more questions than it answers. Though the authors could demonstrate transmission of rhG-CSF across the placenta, they had to borrow data from historical controls to achieve a statistical significance. None in the study group infants had bacterial sepsis (both treated as well as control) and hence the protective efficacy of the presumed biological effect of rhG-CSF against bacterial sepsis remains unproven. It is interesting to note that in 9 out of 11 mothers, preterm delivery could not be delayed beyond 30 h and probably better tocolysis has to be coupled with rhG-CSF administration. Qualitative aspects of neutrophil functions were not assessed. Hence further studies are definitely indicated in continuation of this phase I trial.

G. Karthikeyan,
Assistant Professor of Pediatrics,
Government Kasturba Gandhi Hospital
for Women and children,
Chennai 600 005.

REFERENCES

1. Cairo MS. Therapeutic implication of dysregulated colony-stimulating factor expression in neonates. Blood 1993; 82: 2269-2272.
2. Schibler KR, Liechty KW, White WL, Christensen RD. Production of G-CSF *in vtiro* by moncytes from preterm and term neonates. Blood 1993; 82: 2478-2484.
3. Roberts RL, Szelc CM, Scates SM, Boyd MT, *et al.* Neutropenia in an extremely premature infant treated with rhG-CSF. Am J Dis child 1991; 145: 808-812.
4. Gillian ER, Christensen RD, Ellis R, Vande Ven C, Cairo MS *et al.* A randomized placebo controlled trial of recombinant human granulocyte colony stimulating factor administration in newborn infants with presumed sepsis. Significant induction of peripheral and bone marrow neutrophils. Blood 1994; 84:1427-1433.
5. Gilmore WS, Mckelvey-Martein YJ. Rutherford S. Human milk contains granulocyte colony stimulating factor. Eur I Clin Nutr 1994; 48: 222-224.
6. Medlock ES, Kaplan DC, Cechini M, Ulich TR, del Castillo I, Andresen J *et al.* Granulocyte colony stimulating factor crosses the placenta and stimulates fetal rat granulopoiesis. Blood 1993; 81: 916-922.