

## **Maternal choline supplementation: A therapy for Down Syndrome with population-wide cognitive benefits**

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Down syndrome (DS) is estimated to affect ~400,000 people in the USA, with ~5000 infants born each year with the disorder. DS is caused by the triplication of human chromosome 21 and is the primary genetic cause of intellectual disability. Although DS can be diagnosed prenatally, there are no effective treatments to lessen the intellectual disability or to prevent the early onset of Alzheimer's disease, now known to occur in most individuals with DS. A potential therapeutic strategy emerging from our studies of a trisomic mouse model of DS is to supplement the maternal diet with additional choline, an essential nutrient with many critical roles in fetal neurodevelopment. Our studies demonstrate that maternal choline supplementation (MCS) markedly improves spatial cognition and attentional function in the trisomic offspring, and also protects basal forebrain cholinergic neurons and adult hippocampal neurogenesis. It is currently unknown whether similar benefits would be derived in human DS pregnancies, although anecdotal data from women who have increased choline intake due to our rodent studies are encouraging. The convergence of several factors makes it challenging to conduct a clinical trial of MCS in human DS pregnancies: 1) the majority of DS births are not diagnosed prenatally; 2) prenatal intervention is likely to be critical for MCS benefits to be observed; and 3) most early DS diagnoses end in abortion. Thus, the only way for MCS to widely offer protection to DS individuals would be for all women to increase choline consumption during pregnancy—an intervention likely to benefit typically developing children as well. Currently ~90% of pregnant women consume substantially less than the recommended amount of choline, and choline is absent from most prenatal multivitamins. Rodent studies and a small controlled human intervention study conducted in our lab indicate that choline supplementation during pregnancy is entirely safe and would substantially improve attention, memory and problem-solving for all children. Although confirmation by a larger study is needed, these findings suggest that the addition of choline to standard prenatal vitamin regimens would be beneficial to all children and would also provide a nearly effective intervention for individuals with DS.