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Review Article

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Paracetamol and Cardiac Congenital Malformations in Prediabetic Pregnancy Women

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Abstract

Hyperglycemia can influence the development of the fetal heart, affecting both its structure and its function. Prospective and retrospective cohort studies have demonstrated an increased risk of congenital abnormalities with gestational diabetes. This observation is probably related to the inclusion of women with unrecognized type 2 diabetes [1, 2].

Substantial literature indicates that diabetes in pregnant rats and mice induces embryo lethality, growth retardation and a variable incidence of birth defects. Then, the maintenance of normal concentrations of metabolites from all nutrient classes may be important for prevention of adverse fetal outcome in diabetic pregnancy.

Acetaminophen overdose is the most often cause of acute liver injury and obese women are in particular risk, because is able to induce mitochondrial oxidative stress [3]. Acetaminophen (Paracetamol) over doses decreased embryonic low-molecular-weight thiols (glutathione and cysteine), compounds that play a vital role in the detoxication of exogenous and endogenous chemicals [3-5].

The apparent safety of Paracetamol drug, a useful analgesic only (with no anti-inflammatory properties) is compromised by its widespread and extensive chronic use, particularly in Peruvian population, where its analgesic is doing without control [6-9]. In fact, paracetamol though considered safe at a considerable low dose, especially in women could cause kidney derangement and cardiac malformations during pregnant state if the drug is ingested in the first trimester [8]. Major congenital malformations, including those affecting the cardiovascular system, remain the leading cause of mortality and morbidity in infants of diabetic mothers [10]. Thus, there is overcome potential maternal acetaminophen (paracetamol) toxicity [11].

Hyperglycemia and Cardiac Malformations

Diabetes mellitus in pregnancy is associated with an increased incidence of various congenital anomalies that occur during organogenesis. Pregnancy itself is diabetogenic caused by increased insulin resistance [12, 13]. Presentational diabetes is a major risk factor of congenital heart defects (CHDs).

Animal and human data all point to a role for the diabetic state and elevated insulin resistance in inducing congenital fetal malformations, and free radicals excess and abnormal gene activation have been compromised by week 8 of gestation: the major congenital malformations associated with non-physiological insulin resistance in pregnancy are caudal regression and renal, cardiac and central nervous system abnormalities [14].

Pregestational diabetes resulted in CHDs in 58% of the offspring, including ventricular septal defect (VSD), atrial septal defect (ASD), atrioventricular septal defects (AVSD), transposition of great arteries (TGA), double outlet right ventricle (DORV) and tetralogy of Fallot (TOF). Treatment with NAC in drinking water in presentational diabetic mice completely eliminated the incidence of AVSD, TGA, and TOF and significantly diminished the incidence of ASD and VSD [15].

It's been demonstrated that maternal hyperglycemia caused a dilation of late-gestation fetal ventricular chambers, a reduction of total ventricular myocardial area, and an increase in transversal ascending thoracic aortic area. Glutathione, severely depleted in diabetes is probably, the main causality factor in cardiomyocyte apoptosis, in addition the hyperglycemia [15-17].

Intensive care of the pregnant mother with diabetes has dramatically decreased the incidence of diabetic fetopathy and clinical reports seem to link facial malformations to an increased incidence of sacral-caudal malformations in human diabetic pregnancy [18, 19]. Congenital malformations caused by experimental diabetes can be prevented by antioxidants in vivo that replace the glutathione depletion in mother [20, 21]. Improving the embryonic capability to scavenge oxygen radicals, either by increasing superoxide dismutase activity or by supplying a rate-limiting precursor (N-acetyl cysteine)

for the enhanced synthesis of reduced glutathione, blocks the embryonic dysmorphogenesis [22].

Available data in the literature are limited but support the idea that hyperglycemia may increase adult heart myocardial apoptosis [23]. There has been extensive evidence: maternal hyperglycemia is an inducer of birth defects that include a high incidence of cardiovascular malformations [21, 23].

Maternal diabetes mellitus may cause teratogenesis

There is a significant correlation between maternal hyperglycemia in early pregnancy and the risk of fetal abnormalities in pregnant women with diabetes mellitus, particularly type 1 and non-known-type 2 diabetes mellitus. Fetal abnormalities are strongly associated with higher levels of Hbeta A1-c in the first trimester of pregnancy [24].

Maternal diabetes mellitus is associated with increased teratogenesis, which can occur in pregestational type 1 and type 2 diabetes. Cardiac defects and with neural tube defects are the most common malformations observed in fetuses of pregestational diabetic mothers [25]. It's demonstrated a strong association between maternal obesity and risk of congenital heart defects. This association was present not only for congenital heart defects as a group, but for numerous individual defects. The overall risk increased with increasing BMI [26].

Whereas the sequelae of maternal pregestational diabetes, such as modulating insulin levels, altered fat levels, and increased reactive oxygen species, may play a role in fetal damage during diabetic pregnancy, hyperglycemia is thought to be the primary teratogen, causing particularly adverse effects on cardiovascular development. Fetal cardiac defects are associated with raised maternal glycosylated hemoglobin levels and are up to five times more likely in infants of mothers with pregestational diabetes compared with those without diabetes. The resulting anomalies are varied and include transposition of the great arteries, mitral and pulmonary atresia, double outlet of the right ventricle, tetralogy of Fallot, and fetal cardiomyopathy [25].

Despite improvements in prenatal care, the incidence of congenital malformations in diabetic pregnancies is still 3-4 times higher than in normal pregnancies. These defects could be attributed to alterations of intrauterine environment due to disorder of the maternal metabolism [27]. Glutathione (GSH), a tripe tide implicated in cellular protection against reactive oxygen species, is involved in diabetes-related embryo toxicity interestingly; teratogenicity of maternal serum in diabetic pregnancy is not mediated exclusively by increased concentrations of glucose and ketone bodies as it's demonstrated by Wentzel [28]. Both genetic background and obesity appear to influence the severity of fetal abnormalities in animals [25].

Previous studies in vivo and in vitro have suggested that the oxidative metabolism of the embryo may have a role in the teratogenicity of diabetic pregnancy. In particular, the production of reactive oxygen species by the embryonic mitochondria has been implicated in the teratological process. The induction of congenital malformations by the diabetic milieu occurs during the early embryonic development [29]. Hyperglycemia during organogenesis has a primary deleterious effect on yolk sac function with resultant embryopathy [19].

Diabetes-induced malformations have been often related, both in vivo and in vitro studies, to morphological and physiological alterations of the yolk sac, the principal organ for the passage of nutrients from the mother to the rodent embryo [30]. The embryos explanted from diabetic mothers showed signs of developmental retardation and 16% were morphologically abnormal [31]. Therefore, reduction in embryonic GSH could reduce the protection against the oxidative stress condition described in diabetic pathology.

Norbert Freinkel suggested that the altered fuel mixture offered to the growing conceptus may be the key to most of the changes in the embryogenesis of diabetic pregnancy. He coined the term fuel-mediated teratogens. In vitro and in vivo a high glucose concentration causes embryonic dysmorphogenesis by generation of free oxygen radicals [32]. An enhanced production of such radicals in embryonic tissues is directly related to an increased risk of congenital malformations in occult diabetic pregnancy.

An abnormal handling of reactive oxygen species (ROS) is involved in diabetes-induced dysmorphogenesis in vivo. Indeed, an increased concentration of lipid peroxides, indicating damage caused by ROS, was found in fetuses of diabetes rats. In addition, embryos of diabetic rats had low concentrations of the antioxidant vitamin E compared to control embryos [33].

On the whole, in vivo and in vitro experiments indicate that hyperglycemia itself is not a major factor in producing diabetic embryopathies, but several depletion of tissues glutathione does it herself [30]. Therefore, the proved anti-teratogenic effects of supplementation of superoxide dismutase and N-acetylcysteine in rat embryo culture are supported [22].

It's proved that increased glucose levels caused embryonic maldevelopment in both normal and diabetic serum, and that despite normalization of the diabetic state, the serum from the insulin-treated diabetic rats caused more growth retardation than the no diabetic control serum [28]. Therefore, the pathogenesis of fetal malformations in diabetic pregnancy is multifactorial. Thus, maintaining metabolites from all nutrient classes at a normal level may be important in preventing adverse fetal outcome [34].

In Late Gestation

The rate of heart myocardial apoptosis may increase in adult mice under a hyperglycemic environment, and it's observed both increased apoptosis and necrosis in myocytes, endothelial cells and fibroblasts of the human adult diabetic heart [35-37]. In the fetal context, Gutierrez et al. detected ventricular chamber dilation and myocardial reduction in late gestation fetal hearts, collected from hyperglycemic pregnant CD-1 mouse dams [16, 23].

Paracetamol Danger

Teratogenic potential of diabetes may consist of two components; one associated with 'direct' teratogens perturbing developmental processes in embryos at a 'critical moment' in organogenesis, and a second component, associated with a direct or indirect influence of the diabetic environment on developmental processes in the preimplantation embryos. Thus, there is a threshold glucose level associated with a clear increase of the number of litters with severely malformed fetuses in diabetics' animals [38]. Maternal hyperglycemia altered morphology of the late-gestation fetal mouse heart [16].

Mitochondrial alterations produced by oxidative stress have been described in embryos developing in a diabetic environment. Interestingly, it's been demonstrated recently, that Paracetamol in normal doses may be able to induce mitochondrial oxidative stress [3]. Furthermore, oxygen radicals-scavenging enzymes can reduce the embryo toxic effects induced by diabetic conditions [31].

Acetaminophen overdose is the most often cause of acute liver injury. The toxic mechanism is linked to formation of an active metabolite that reacts with glutathione generating acetaminophen-glutathione conjugate (APAP-SG). This compound has been recognized to be non-toxic generally. Recent studies showed, however, that APAP-SG could possess a toxic effect too, particularly in obese women [3].

Liver glutathione stores become depleted with paracetamol overdoses –chronic use- so that the liver is unable to deactivate the toxic metabolite (NAPQ1) [39]. The paracetamol induced renal damage in pregnant women results from a mechanism similar to that which is responsible for hepatotoxicity; this mechanism is probably participate in cardiac malformations in an early pregnant state [40].

In this context, the worldwide use of paracetamol as a household analgesic, including during pregnancy may be dangerous: in fact, fetal tissues (and maternal) can be adversely affected by paracetamol and are potentially dangerous in the presence of chronic abdominal obesity (pathological insulin resistance) where liver and tissues antioxidant glutathione is reduced [6, 41].

Prevention

Animal models have been used to study the expression patterns of many genes that contribute to structural defects in the heart, although <10% of these underlie congenital cardiac defects in humans [42-44]. Intrauterine under- or over nutrition alters offspring cardiac structure and function. The expression of cardiac-specific genes is likely altered reflecting impaired cardiac insulin signaling that contributes to cardiac insulin resistance that often precedes cardiovascular disease [44].

Congenital malformations occur despite good glycemic control, thereby confirming a role for reactive oxygen species ROS and inflammatory and oxidant environment, or a lack of antioxidant protection enough, as glutathione, Vitamin E and Selenium [33, 45].

Daily oral natural vitamin E (gammatocopherol) may improve insulin action because it restores more appropriate plasma reduced glutathione, improving antioxidant cellular status and improving pancreatic b cells response to glucose in healthy and prediabetic subjects [46]. Thus, enhancing synthesis of reduced glutathione blocks the embryonic dysmorphogenesis, but not in cardiac malformations, because fetal heart was found to be hypertrophic (resorption rate in fetal organs tended to be decreased with the increased dosage of vitamin E) [20, 22]. Then, maternal administration of vitamin E can prevent congenital malformations in mid and late pregnancy, not in the early pregnancy. In comparison, Selenium may offer other additional advantages: its powerful antioxidant properties preserve reduced glutathione because its role in the major intracellular antioxidant enzyme the glutathione peroxidase. But Peruvian mothers' don´t consume neither diary selenium nor vitamin D.

In addition, it is been demonstrated that acute glutathione depletion causes severe hypertension in normal rats: Since Paracetamol causes physiological reduction of glutathione, we don´t surprise that this drug may increase blood pressure in advanced insulin resistant humans. Therefore, pregnant women must be caution before taking this drug, but never without medical indication. A recent investigation has found transcriptomic changes in full-genome human miRNA expression and immune modulating effects and oxidative stress responses to paracetamol even at low doses [47-50].

Most severe malformations occurs during organogenesis, period that is completed by sixth week after conception, and thus, the critical period for malformations is almost over by the time pregnancy becomes clinically apparent: in fact, organogenesis is completed before women recognize that they are pregnant; therefore, the precounseling and strict planning of pregnancy too in prediabetic women or gestational diabetes, become an urgent need.

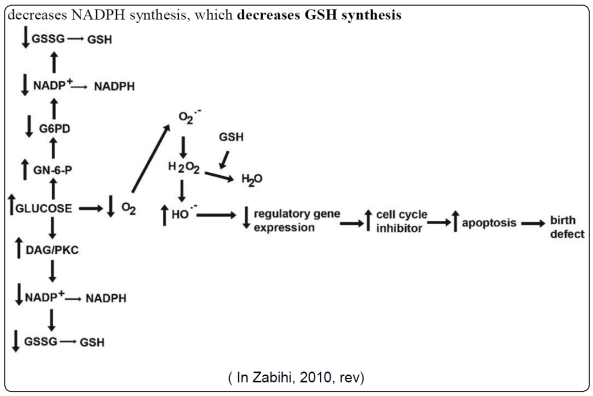
Conclusion

Because a reduction of glutathione levels in cells has been found to increase the risks for diseases and poisoning, Paracetamol is potentially dangerous in pregnant women. Pre-gestational maternal diabetes is associated with strong teratogenic effects on the kidney, urinary tract, and heart, and strongly associated with multiple congenital abnormalities [51]. Pre-conception recognition of women at high risk for type 2 diabetes and optimal glycemic control may reduce the risk of congenital anomalies. A healthy diet and regular exercise and reduction in paracetamol-toxicity in a subclinical way, may help optimize pre-pregnancy weight and reduce the risk of congenital anomalies [52, 1].

Paracetamol may increase the risk of cryptorchidism and asthma during childhood as well as preeclampsia, maternal phlebothrombosis and pulmonary embolism as it's recently reported [53]. In the presence of established diabetes, It is must be stress the importance of a strict metabolic control, started well before conception, to prevent excess rates of congenital malformation, and the intensive insulin therapy must be considered as an first option in this regard [54].

In diabetic women who is thinking to pregnant, an optimal metabolic control must been established, and the danger of paracetamol use must be informed [55-60]. Maternal hyperglycemia influence the development of the fetal heart, affecting both its structure and its function, and Paracetamol may be aggravated. Acetaminophen (Paracetamol) is one of the most common causes of poisoning worldwide, in particular in the patients with low amount of the hepatic glutathione, that is, insulin resistant and diabetic patients [60-66].

Biochemical/molecular pathway by which maternal hyperglycemia may cause birth defects Excess glucose transported to the embryo is metabolized. Increased glycolytic flux stimulates glucosamine-6-PO4 synthesis (GN-6-P), which inhibits G6PD activity, which decreases NADPH synthesis, Which decreases GSH synthesis



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