Interview Dr. Patrick Catalano

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Patrick Catalano is a Professor and Vice Chair of Obstetrics and Gynecology at Tufts University School of Medicine and a Maternal -Fetal Medicine specialist at Tufts University Medical Center. His research is focused on maternal metabolism in women whose pregnancies are complicated by diabetes and obesity. Further he is studying the short and long-term effects on mothers and their children. He has had continuous funding from the Eunice Kennedy Shriver National Institutes of Child Health and Human Development for the past 30 year. Title(s): Vice Chair of Obstetrics & Gynecology Research; Principal Investigator, Mother Infant Research Institute; Professor, Tufts University School of Medicine, Friedman School of Nutrition, Science and Policy; Professor, Clinical and Translational Institute (CTSI). Department: Mother Infant Research Institute. Clinical Focus Areas: Maternal metabolism in women whose pregnancies are complicated by diabetes and obesity, the short and long-term effects on mothers and their children. Research Focus Areas: His research program is focused on a Lifestyle Intervention in Preparation for Pregnancy (LIPP). This is a RCT that is being conducted at Tufts Medical Center, the Pennington Biologic Research Center and Case Western Reserve University. The intervention is a lifestyle intervention of healthy eating (Mediterranean diet) and exercise to have overweight/obese subjects in the intervention group decrease their weight 5-7% based on pre-pregnancy weight from their prior pregnancy as compared to a control or usual care group. The Program in Boston will be

conducted at Tufts Medical Center and the Human Nutrition Research Center on Aging (HNRCA). The study is funded by NICHD.

1. Initially, we would like you to briefly explain to us the problem of Gestational Diabetes Mellitus? How can it be prevented?

Prof. Patrick: Gestational diabetes mellitus (GDM) can best be prevented by improving metabolic health of the individual prior to a planned pregnancy. The general guidelines for this are a healthy nutrition, specifically avoidance of simple sugars, saturated fats, and excess calories. The second component is having a healthy, active lifestyle which includes increased physical activity depending on the constraints of the individual. Lastly, if an individual is overweight or obese, improvement in weight by 5-7% has been shown to improve metabolic health in addition to the lifestyle measures of healthy eating and exercise.

2. Now taking advantage of the specific knowledge, regarding your research and publications, in the article "Trying to understand gestational diabetes "[1], you state "that the metabolic dysfunction in obese women at risk for gestational diabetes did not start in the third trimester, when the clinical diagnosis of gestational diabetes is usually made, but the pathophysiology starts in the first trimester". What are the implications of this statement? Is it possible to have a diagnosis before the third trimester? What would be the advantages regarding pathophysiology and its possible consequences?

Prof. Patrick: Classically, the definition of gestational diabetes is made between 24 and 28 weeks' gestation. Many investigators over the last few years have attempted to apply the criteria of gestational diabetes at 24-28 weeks' gestation in early pregnancy but the results are inconclusive. While the metabolic abnormalities that lead to the development of gestational diabetes such as decreased insulin sensitivity and pancreatic b-cell function and inflammation are present prior to conception and made worse with advancing gestation, the criteria to make the diagnosis of gestational diabetes in early pregnancy have not yet been well defined. Many individuals have been examined looking at HbA1c or other factors with mixed results. There is a

study supported by the NIH trying to determine what the criteria are for gestational diabetes in early pregnancy, and this is available on clinicaltrials.gov. The study is entitled GO MOMS.

3. Students and researchers who want to understand Gestational Diabetes Mellitus must understand basic biology, as demonstrated in the article you co-authored "Cellular Mechanisms for Insulin Resistance in Normal Pregnancy and Gestational Diabetes" [2]. Can you tell us a brief explanation of the relationship between cell biology and this problem? Also offer us clues what gaps we still need to understand about this relationship, to inspire future researchers.

Prof. Patrick: The followed article references the cellular defects of skeletal muscle leading to increased insulin resistance in individuals who are pregnant and those with gestational diabetes. Defect in insulin resistance in skeletal muscle is a post-receptor defect. https://diabetes.diabetesjournals.org/content/48/9/1807 and https://www.researchgate.net/publication/12818751_Friedman_JE_Ishizuka_T_Shao_J_Huston_L_Highman_T_Catalano_P_Impaired_glucose_transport_and_insulin_receptor_tyrosine_phosphorylation_in_skeletal_muscle_from_obese_women_with_gestational_diabetes_Diabe .

4. Gestational Diabetes Mellitus has short- and long-term consequences for the fetus and the mother, as you present in the article: Gestational Diabetes and Insulin Resistance: Role in Short- and Long-Term Implications for Mother and Fetus [3]. Synthesize for us what these consequences are? And what ways the research are pointing to avoid these evils?

Prof. Patrick: The underlying problem of gestational diabetes relates to associated problems of increased insulin sensitivity, inflammatory profile, risk of hypertensive disorders, coagulation defects, risk of venous thromboembolism and increase in lipid profile. For the fetus, gestational diabetes results in increased insulin resistance which allows for excess nutrient availability in the fetus, not only for glucose but also lipid moieties. Increased fetal adiposity increases the risk of childhood obesity as well as adult obesity. Based on the HAPO Follow-up Study, maternal obesity primarily increases the risk of childhood obesity. Maternal metabolic dysfunction relating to the development of gestational diabetes then increases the risk of metabolic dysfunction in the offspring. These are not exclusively distinct issues;

there is overlap between the two. The best way to avoid these problems is related to the response to question #1.

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5. Still referring to the article in the previous question: Gestational Diabetes and Insulin Resistance: Role in Short- and Long-Term Implications for Mother and Fetus, you and the other co-authors point to an increase in the incidence of Gestational Diabetes Mellitus. What are the likely reasons? Why have migrants from less developed regions shown differentially high numbers?

Prof. Patrick: Increase in the obesity epidemic in all regions of the world increases the risk of problems related to insulin resistance and inflammation, hallmarks of development of gestational diabetes. There may also be genetic predisposition, for example the thrifty gene hypothesis, whereby development of insulin resistance may be an adaptive mechanism in times of famine, whereby change in environment with ready access to processed foods may increase the risk of the development of obesity and metabolic dysfunction. In the United States, the example of the Pima Indian population in Arizona exemplifies this problem.

6. In your article "Gestational diabetes mellitus [4]", published in one of the world's most important scientific journals, you and the co-authors point out that gestational diabetes is very frequent, but it is very common that hyperglycemia is not diagnosed. How difficult is it to discover gestational diabetes? What makes it so difficult to identify?

Prof. Patrick: The reason for this is that currently the diagnosis of gestational diabetes is made using 75 or 100 gram glucose tolerance test using the criteria of the WHO or the IADPSG. The use of HbA1c in mid to late pregnancy is not a sensitive or specific marker for the diagnosis of gestational diabetes. Hence it is difficult for many populations to arrive in a fasting condition to have a formal glucose tolerance test using either of the above criteria.

7. The combination of maternal obesity and gestational diabetes proves to be serious for the health of the pregnant woman and the fetus, as shown in your article "The Hyperglycemia and Adverse Pregnancy Outcome Study" [5]. Explain us why this combination is so harmful?

Prof. Patrick: The reason for this is that it is possible to have insulin resistance and a b-cell defect and not be obese. On the contrary, one can have overweight or

obesity but not have evidence of insulin resistance or a b-cell defect. Many people term the later as the metabolic healthy obese individual. However, the combination of both increases the risk of metabolic dysfunction, including hyperlipidemia and inflammation. While individually the problems are a risk for the patient, the combination of both increases the risk because of not only the overlap of metabolic dysfunction but the individual adverse components of each make the combination greater than the sum of the individual factors.

8. In your article “Fetuses of obese mothers develop insulin resistance in utero” [6], you talk about the risks of the baby being born obese and developing insulin resistance because of Gestational Diabetes. Tell us about these risks and what you have found in your research to prevent these consequences.

Prof. Patrick: What we have observed in our research is that the incidence of women with gestational diabetes and/or obesity is that the infants that have increased weight specifically rated to increase in adiposity. On examining cord blood estimates of insulin resistance (HOMA-IR) in women whose pregnancies are complicated by obesity, the babies have higher insulin resistance at the time of birth, which we believe increases the risk of metabolic dysfunction in later life. The HAPO follow-up Study has shown that offspring of those women who had gestational diabetes in pregnancy, which was not treated because this was an observational study, at age 8-11 have evidence of increased insulin resistance and a trend for increase in b-cell dysfunction independent of the BMI of the child in adolescence.

9. In your vast experience in research in obstetrics and all related topics, such as gestational diabetes, give us hints about the areas or topics that you consider "hot" for future research in the field of pregnant and fetal health, thinking about future health researchers.

Prof. Patrick: While treatment of gestational diabetes is certainly an area of research interest, at present we are limited to the use of insulin and the consideration of the use of oral agents such as metformin and/or glyburide. While many organizations prefer the use of insulin because it does not cross the placenta, long-term effects of the oral agents continue to be debated. My own personal take on this question is that rather than focus on treatment, one ought to focus on prevention. I would refer you to a study that is ongoing in our

laboratory called the Lifestyle Interventions in Preparation for Pregnancy or LIPP that I have attached a copy of in my response to these questions.

10. We have found many scientific publications from you in high-level journals, and many of these texts have multiple co-authors. We would also like you to give us tips regarding high quality academic production and how to establish productive partnerships, thinking about young students who are interested in pursuing a fruitful academic career.

Prof. Patrick: One first needs to be in an academic environment where there are mentors able to provide guidance and insight to young investigators. For my own career, one looks at reference 1 trying to understand gestational diabetes and Diabetic Medicine in 2014. One can see that these mentors need not be in one's own particular field of interest. For me, my mentor was an obstetrician whose particular interest was longitudinal study design. Other mentors' experience was related to assessment of various techniques, for example Dr. Sims introduced me to the use of a hyperinsulinemic-euglycemic clamp procedure. Other examples are Dr. Boyd Metzger, who was very helpful relating to the issue of large observational studies and people like Dr. Emilio Herrera were very important relative to assessing lipid metabolism in the development of gestational diabetes. Last, I think that establishing collaborators in basic sciences is an important component for translational research. While theoretically one could try to master both areas, for me colleagues who are basic scientists like Dr. Gernot Desoye and Dr. Sylvie Hauguel-de Mouzon. The bottom line is having good mentors, having a diverse background with different points of view and the ability to stay focused in one's area but not to the point of becoming a reductionist and putting all of one's hypotheses in one specific area. Also one needs to be open to what is going on in the literature. For my own part, I have not developed an expertise in genetics or epigenetics, and even for established investigators there are always areas that one could learn more about to further their research.