

<b>Institution:</b> Queen's University Belfast
<b>Unit of Assessment:</b> 2
Title of case study: Changing the International Criteria for the diagnosis of Diabetes in Pregnancy
<p><b>1. Summary of the impact</b></p> <p>New criteria for the diagnosis of diabetes in pregnancy have been developed by the International Association of Diabetes in Pregnancy Study Groups and adopted by the American Diabetes Association on the basis of the Hyperglycaemia and Pregnancy Outcomes (HAPO) study. These new criteria double the percentage of women diagnosed with diabetes in pregnancy from approximately 8.5% to 17%. Appropriate management improves outcomes for them and their new born children. The results, which proved valid for all ethnic groups and countries, have led to a worldwide re-appraisal of glycaemic risk in pregnancy and the introduction of new guidelines to manage this.</p>
<p><b>2. Underpinning research</b></p> <p>Researchers in Belfast had a long-standing interest in the impact of high glucose in pregnancy, which led to a series of papers from the late 1980s describing the harmful effects of elevated maternal glucose on both mother and baby, and suggesting that new criteria for the diagnosis of diabetes in pregnancy might be required<sup>1,2</sup>. Elizabeth Trimble (Professor of Clinical Biochemistry) and David Hadden (Honorary Professor of Diabetic Medicine) were key to this. As a consequence, researchers at Queen's University Belfast were lead participants in discussions with other leading international research groups that led to the development of the protocol for the Hyperglycaemia and Pregnancy Outcome (HAPO) study. This major international study involved a total of 25,505 pregnant women at 15 centres in nine countries, who underwent 75-g oral glucose-tolerance testing at 24 to 32 weeks of a pregnancy. The study was led by Dr. Boyd Metzger from North-Western University in the USA and funded by a grant from the US National Institute of Health (NIH). Queen's investigators were co-applicants on the successful proposal, which was led from Chicago, and were members of the study Steering Committee, Head of the Central laboratory (Professor Elisabeth Trimble), Head of the European Clinical Area (with 3 separate clinical centres) (Professor David Hadden) and Co-chair of the Publications Committee (Professor Elisabeth Trimble). Belfast provided the Central laboratory for the study, because of its long and wide experience in measuring peptides in clinical samples developed under the leadership of the late Professor Keith Buchanan. This laboratory performed the analysis of samples from all countries for the key parameters of glucose, insulin and C-peptide. In addition, Belfast was one of the key recruitment centres for the study.</p> <p>The main results of the HAPO study were published in the New England Journal of Medicine in 2008 with three Queen's staff among the 14 authors<sup>3</sup>, and subsequently, a number of secondary publications appeared in other journals<sup>4,6</sup>. The main findings of the HAPO study were as follows: maternal glucose levels, even though these were below those diagnostic for diabetes, strongly correlated with the main outcomes of (i) increased birth weight of the baby, (ii) an increased need for primary Caesarean section, (iii) clinically evident low blood glucose in the newborn child and (iv) increased cord-blood insulin levels. In addition, maternal obesity also affected the main outcomes independent of the mother's elevated blood glucose levels. Obesity together with elevated blood glucose increased the risk for undesirable outcomes round the birth of the baby. The results proved to be valid for all ethnicities and geographical regions tested.</p>

In summary, the global relevance of the risk revealed by the HAPO study combined with emerging evidence that intervention at lower plasma glucose levels leads to improved outcomes, has lent great urgency to re-evaluation of risk levels in 'gestational diabetes' and the development of new guidelines for risk management.

### 3. References to the research

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2. McCance DR, Hanson RL, Pettitt DJ, Bennett PH, Hadden DR, Knowler WC. Diagnosing diabetes mellitus--do we need new criteria? *Diabetologia*. 1997; 40 (3): 247-55. DOI: 10.1007/s001250050671 (*article cited 65 times*).
3. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks DA. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008; 8; 358 (19): 1991-2002. DOI: 10.1056/NEJMoa0707943 (*Article cited 586 times*).
4. Metzger BE, Persson B, Lowe LP, Dyer AR, Cruickshank JK, Deerochanawong C, Halliday HL, Hennis AJ, Liley H, Ng PC, Coustan DR, Hadden DR, Hod M, Oats JJ, Trimble ER; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcome study: neonatal glycemia. *Pediatrics*. 2010; 126 (6): e1545-52. DOI: 10.1542/peds.2009-2257 (*article cited 9 times*).
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6. HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. *Diabetes*. 2009; 58 (2): 453-9. DOI: 10.2337/db08-1112 (*article cited 94 times*).

### Funding

Central Laboratory of HAPO Study. Principal Investigator: **Professor Elisabeth Trimble**  
 Sponsor: **North Western University (USA)**; duration: 08/08/2000 – 28/07/2009  
 From **NIH**: total \$18.0 million: of which \$2.36 million to Central Lab at Queen's  
 From **American Diabetes Association** total \$1.37 million: of which \$ 0.5 million to Central Lab

#### 4. Details of the impact

The HAPO study identified for the first time, on a global basis, the adverse impact on both mother and baby of mildly elevated levels of glucose below those traditionally used to make a diagnosis of diabetes in pregnancy. The traditionally used criteria for diabetes in pregnancy were based on the principle of identifying women at risk of diabetes after the pregnancy, rather than the principle of identifying pregnancies where there was significant risk to mother and/or baby as a consequence of elevated glucose. HAPO aimed to determine the level of maternal glucose associated with abnormal pregnancy outcomes for mother and baby, and hence to allow the development of new criteria for the diagnosis of diabetes in pregnancy.

Following the publication of the major HAPO results in 2008, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) convened a consensus panel, which published new recommended criteria for the diagnosis of diabetes in pregnancy based on the HAPO study findings, in *Diabetes Care* in 2010<sup>1,2</sup>. Queen's researchers were members of the Consensus Panel which published the recommendations and are amongst its authors. The new criteria are based on identification of average glucose values at which odds for increased birth weight, levels of insulin in cord blood and percentage body fat of the baby in the top 10% reached 1.75 times the estimated odds of these outcomes at average glucose values. Therefore, the whole basis on which the diagnosis of diabetes in pregnancy is made has been changed from risk of subsequent diabetes in the mother, to risk to the baby at birth.

The new criteria have already begun to have far reaching consequences at an international level<sup>1,3</sup>. A completely new two phase screening strategy for diabetes in pregnancy is recommended. This consists of an initial measurement of fasting plasma glucose, random glucose or HbA1c (a test that indicates average blood glucose levels over the past three months) in all women at the first prenatal visit. If the results are abnormal, the woman is managed as if she had diabetes preceding pregnancy. In all women with normal results at this initial visit, it is proposed that a 2 hour 75 g oral glucose tolerance test is carried out at between 24 and 28 weeks gestation, and new criteria are provided for the diagnosis of gestational diabetes. In a typical developed population, use of the new criteria approximately doubles the percentage of women who will be diagnosed as suffering from gestational diabetes, from 8% to 16%. Appropriate management of women with this condition improves outcomes both for mother and baby.

The new criteria for diabetes in pregnancy were endorsed by the American Diabetes Association in January 2011 and are currently under review by many other national guideline bodies. There is widespread acceptance that the HAPO results indicate the need for change in glycaemic management during pregnancy. The problem is addressed in a very large number of papers, reflecting on how to implement the changes in management in many countries, This is the case for example in China, Japan, Australia, New Zealand, India, Israel, Germany, Switzerland, UK, USA and Canada. The IADPSG guidelines have been accepted or endorsed in part or whole by many bodies including the American Diabetes Association, the Japanese Diabetes Pregnancy Society, the Australasian Diabetes in Pregnancy Society (Australia and New Zealand)<sup>4</sup>, and the Italian Diabetes Pregnancy Society<sup>5</sup>.

#### 5. Sources to corroborate the impact

1. International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*, 2010; 33 (3):676-682. DOI: 10.2337/dc09-1848.

*The proposed new international criteria for diagnosis of diabetes in pregnancy based*

*on the HAPO study.*

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*A rapid assessment of the relevance of HAPO for the UK National Screening Committee*
3. Holt RI, Coleman MA, McCance DR. The implications of the new International Association of Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria for gestational diabetes. *Diabet Med.* 2011, 28 (4):382-5. DOI: 10.1111/j.1464-5491.2011.03236.x.
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5. Paglia MJ, Coustan DR. Gestational diabetes: evolving diagnostic criteria. *Curr Opin Obstet Gynecol.* 2011, 23 (2):72-5. DOI: 10.1097/GCO.0b013e328342d21e.