Discovery, Knowledge, and Action—Diabetes in Pregnancy Across the Translational Spectrum: The 2016 Norbert Freinkel Award Lecture

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The Norbert Freinkel Award is given in memory of Norbert Freinkel, a dedicated and insightful investigator and gifted writer, to honor a researcher who has made outstanding contributions, including scientific publications and presentations, to the understanding and treatment of diabetes in pregnancy. H. David McIntyre, MD, FRACP, Director of Obstetric Medicine at Mater Health Services and Head of the Mater Clinical Unit at The University of Queensland in Brisbane, Australia, received the prestigious award at the American Diabetes Association's 76th Scientific Sessions, 10–14 June 2016, in New Orleans, LA. He presented the Norbert Freinkel Award Lecture, "Discovery, Knowledge, and Action—Diabetes in Pregnancy Across the Translational Spectrum," on Saturday, 11 June 2016.

Pregnancy complications related to diabetes remain a major cause of maternal and fetal morbidity in the short term and serve as antecedents and predictors of long-term risks of diabetes, obesity, and more widespread metabolic dysfunction in both mother and child. This article aims to outline major areas of active research, well-established scientific knowledge, and the ongoing challenge of translating basic and clinical research findings into everyday clinical practice. The view presented is somewhat iconoclastic, based on the author's experience across multiple research domains. A variety of models attempt to describe the "translational spectrum" (1,2). Several principles underlie such models: *1*) that basic scientific evidence should be the foundation stone of clinical practice, *2*) that bench to bedside to clinic translation is essential, and *3*) that clinical observations may feed back into novel basic research questions. Further, it is frequently noted that the entire translational process is fraught with multiple difficulties that may obstruct or delay the overall goal of improving individual and population health.

DISCOVERY

The physiologic development of insulin resistance during human pregnancy has long been recognized as an important underlying cause of hyperglycemia with advancing gestation. Professor Norbert Freinkel, in his celebrated 1980 Banting lecture, "Of Pregnancy and Progeny" (3), stated: "the hypoglycemic potency of insulin is diminished [in pregnancy] as insulin resistance supervenes." Freinkel further stated: "islet secretory performance is augmented." However, both the latter statement and the maintenance of normal glucose homeostasis in pregnancy depend on adaptive

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augmentation of islet functional capacity to meet the metabolic demands of pregnancy.

Freinkel described a number of hormones (human chorionic gonadotropin, progesterone, human placental lactogen, and estrogen) that increased temporally across human gestation and were potential mediators of pregnancy insulin resistance, as further evidenced by their ability to produce insulin resistance in experimental models in humans (4–6). Despite this and the subsequent work of Ryan and Enns (7) and Kühl (8), the underlying mediators in insulin resistance in pregnancy remained incompletely explained.

Growth hormone–like activity has long been described in the human placenta (9). In 1985, a specific placental ("variant") growth hormone (PGH) was discovered by Hennen et al. (10) and noted both to progressively replace pituitary ("normal") growth hormone (GH-N) and to rise to high and sustained levels in the maternal circulation from mid-gestation onwards (11). Given the known action of GH-N to increase insulin resistance outside pregnancy, as witnessed in acromegaly, a potential role for PGH in pregnancy-related insulin resistance appeared plausible (12). At the same time, knowledge of GH binding proteins was expanding. Initial investigations in murine pregnancy showed that the pregnancy-related increase in GH was matched by an increase in GH binding, meaning that free GH concentrations rose only marginally (13).

In light of these discoveries, we investigated the temporal profiles and potential physiologic roles of PGH and the high-affinity growth hormone binding protein (GHBP) in human pregnancy. Our initial publication (14) demonstrated that in contrast to murine pregnancy, GHBP fell progressively during human pregnancy, suggesting a different physiology.

Subsequently, our group demonstrated increased PGH over the course of human gestation. In tandem with the previously described decrease in GHBP, this equated to an increase in free PGH, in marked contrast to the murine findings (15). We also demonstrated much lower concentrations of free PGH in pregnancies complicated by fetal growth restriction, with a tendency to higher concentrations in babies with accelerated growth. A secondary analysis of those women with type 1 or type 2 diabetes and available home blood glucose testing records showed a positive correlation between 28-week PGH and postprandial glycemia, providing some support for a potential role of PGH in modulating insulin resistance (15).

Potential regulation of PGH concentrations in pregnancy remained unclear, with one small study (16) describing an increase in PGH after insulin-induced hypoglycemia (analogous to the changes in GH-N outside pregnancy). We assessed changes in PGH over the course of an oral glucose tolerance test (OGTT) (17) and noted that in contrast to the normal nonpregnant state but similar to the acromegalic state (12), there was no suppression of PGH following oral glucose loading.

Subsequent investigations by Barbour, Friedman, and colleagues (18) in Colorado, using a transgenic mouse model, demonstrated that supraphysiologic concentrations of human PGH were associated with severe insulin resistance related to overexpression of p85 (19,20), lending further credence to a potential role of PGH in modulation of insulin resistance. In a larger-scale cross-sectional study, we then sought to evaluate which maternal hormonal and metabolic factors were associated with variations in insulin sensitivity in human pregnancy (21). Perhaps disappointingly for those "devoted" to PGH as the primary modulator of insulin resistance, this study showed only a weak and statistically insignificant association between PGH and OGTT-derived insulin sensitivity as estimated by the Matsuda index (22). Of the factors assessed, maternal serum leptin, insulin-like growth factor binding protein 1, and triglycerides were most strongly associated with cross-sectional variability in insulin sensitivity in the cohort. No difference in insulin sensitivity was found between women with potential gestational diabetes mellitus (GDM) and those with normal glucose tolerance according to post hoc International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (23) classification.

In summary, although insulin resistance appears to be a fundamental physiologic process in normal human pregnancy, the mechanism(s) underlying its development and the differences in the degree of whole-body insulin resistance between women during pregnancy remain incompletely understood. PGH, given its tonic, nonpulsatile secretion and supraphysiologic concentrations, particularly in late gestation, may contribute to the overall "diabetogenic" environment of pregnancy, but its role is clearly neither primary nor closely regulated. An improved understanding of the basic mechanisms underlying pregnancy insulin resistance may help in developing future therapeutic options in diabetes in pregnancy.

KNOWLEDGE

The second thread that I would like to weave into my narrative concerning diabetes in pregnancy involves the large body of data (n = 23,316 blinded participants) collected in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (24) and its subsequent use in global attempts to develop a consensus regarding the definition of GDM related to the risk of adverse pregnancy outcomes. Previously, GDM had been defined largely in relation to the postpartum risk of maternal progression to "frank" diabetes. The landmark study of O'Sullivan and Mahan (25), used as the primary source for this definition, involved a small cohort of 676 women recruited in Boston in the late 1950s and subsequently followed up to ascertain whether they had developed diabetes following their index pregnancy.

The HAPO study clearly demonstrated that the risks of complications classically associated with known preexisting diabetes complicating pregnancy extended down to levels of glycemia previously considered "normal" and further that the relationship between various measures of glycemia and these risks were near linear and without any discernible threshold(s) or inflection point(s), which would suggest "natural" diagnostic cut points.

Although the HAPO data have greatly increased our knowledge regarding hyperglycemia in pregnancy, their translation into clinical recommendations/guidelines was by definition a consensus-driven process. The IADPSG convened a consensus conference in 2008, 1 year after the initial presentation of the HAPO study data, to attempt to both review HAPO and other available studies and to derive a consensus definition of hyperglycemia in pregnancy. This led to the IADPSG recommendations, published in 2010 (23), and to ongoing debate since that time. The guiding principle of the IADPSG document was that women at a similar risk (after

statistical correction for other factors—in particular, obesity) of hyperglycemia-related complications of pregnancy should be treated in a similar manner. Minimal dissent has been raised regarding this underlying principle, but its practical application has proven extremely challenging. The empirical consensus choice of diagnostic thresholds corresponding to an adjusted odds ratio of 1.75 as compared with the HAPO cohort mean for large-for-gestational-age (LGA) babies, excess neonatal adiposity, and neonatal hyperinsulinemia to determine OGTT thresholds for the diagnosis of GDM has prompted controversy. Dissent has been based on alternative, geographically diverse, historical, and empirical arguments. At the time of writing, full consensus remains elusive, restrained largely by pragmatic concerns regarding what is perceived as "too much" GDM if the IADPSG criteria were to be fully implemented.

The concept of "too much" GDM implies that a reasonable or "right" prevalence of GDM exists. Data from the National Health and Nutrition Examination Survey (NHANES) in the U.S. (26) suggest that in women aged 18–44 years, the prevalence of known or undiagnosed type 2 diabetes is 4.5% and that of impaired fasting glucose and/or impaired glucose tolerance is 26.4%, corresponding to a total prevalence of abnormal glucose metabolism in this group of 30.9%. In light of this finding, the observed (post hoc) prevalence of GDM (ranging from 17.3 to 25.5%) using IADPSG criteria across the HAPO U.S. centers (27) appears reasonable rather than excessive.

Given that the IADPSG recommended diagnostic thresholds for GDM and those developed by Carpenter and Coustan (28) (and widely used in the U.S.) are numerically very similar (Table 1), other factors clearly act to lower the prevalence of GDM when alternative testing strategies such as those advocated by the American College of Obstetricians and Gynecologists (ACOG) (29) are used. Two such factors are evident—first, the use of two-stage testing with a preliminary nonfasting glucose challenge test (GCT) before a diagnostic OGTT and, second, the requirement that two glucose measures should exceed the diagnostic thresholds for a diagnosis of GDM to be made. With regard to two-step testing, a systematic review in 2012 showed that this failed to detect ~26% of GDM cases (30). With regard to the "two abnormal values" rule, multiple epidemiologic studies have demonstrated that one abnormal value carries similar risks of pregnancy complications (31) and one randomized controlled trial (RCT) has demonstrated treatment benefits if such women are labeled as having GDM and treated accordingly (32).

Table 1—Diagnostic strategies for GDM (generally at 24–28 weeks of gestation)

	ACOG/CC	IADPSG
Process	Two steps: nonfasting 50-g GCT followed by 100-g OGTT	One step: universal 75-g OGTT
GDM diagnostic thresholds (mg/dL)		
Fasting	≥95	≥92
1 h	≥180	≥180
2 h	≥155	≥155
3 h	≥140	N/A

ACOG (29)/CC (28) process and criteria for GDM compared with the IADPSG process and criteria (23). In the ACOG/CC process, an initial GCT with 50 g glucose and 1-h postload glucose measurement is used, with variable thresholds (130–140 mg/dL) for progression to formal fasting 100-g OGTT. The ACOG/CC process requires two values greater than the threshold for GDM diagnosis, whereas one value greater than the threshold is sufficient for diagnosis by IADPSG criteria. ACOG also accepts GDM diagnosis by the National Diabetes Data Group (NDDG) criteria, which use higher threshold values (48) (data not shown). N/A, not applicable.

A further common argument against the IADPSG diagnostic criteria is that they have yet to be formally evaluated in an RCT. As is well known, two large RCTs of treatment of GDM have been conducted (33,34). The baseline characteristics of the women included in those trials have been compared with a theoretical cohort derived from the HAPO study cohort after post hoc classification using the IADPSG criteria in Table 2 (26). Clearly, the women in the RCTs and those with "IADPSG GDM" from HAPO are similar in many ways (in particular in terms of mean age, BMI, and fasting glucose), although their postload OGTT values vary in a predictable way given the particular inclusion and exclusion criteria used in the RCTs.

Personally, I do not believe that equipoise exists for a further RCT conducted using strict IADPSG criteria for inclusion. Such a trial would likely end up recruiting a cohort substantially similar to those women who have previously been studied. Given that the previous RCTs took 10 (33) and 6 (34) years, respectively, to complete and gave largely congruent results, I do not consider a further RCT to be justified. The benefits of GDM treatment are supported by systematic reviews of available studies (35,36). Nonetheless, opinions vary strongly on this topic and a further study (with a positive result) may well be required if long-entrenched practices in the U.S. are ever to change.

Several approaches, short of conducting "the definitive" RCT, have been used to attempt to define the potential impact of changing from local historical GDM criteria to those recommended by IADPSG. Two groups have now also reported "whole of hospital" outcomes related to GDM after changing from a two-step "Carpenter and Coustan" (CC) diagnostic approach to the one-step IADPSG

Table 2—Mean characteristics of women with GDM across study cohorts

Study	Crowther et al. (33)	Landon et al. (34)	HAPO post hoc with IADPSG criteria (26)
Age (years)	30.5	29.1	31.0
BMI (kg/m^2)	26.4	30.2	29.9
OGTT glucose (mg/dL)			
Fasting	86	86	88
1 h	N/A	193	173
2 h	155	175	137
3 h	N/A	137	N/A

Comparison of mean characteristics of women with GDM who were included in two pivotal RCTs of GDM treatment and those who would have been diagnosed with GDM in the HAPO cohort if IADPSG criteria had been used. Note that BMI was calculated using early pregnancy height and weight measurements in the Crowther trial and from measurements at the time of the OGTT in the Landon and HAPO studies. N/A, not applicable.

approach, and these studies deserve close consideration. Duran et al. (37) from Madrid reported pregnancy outcomes for their entire birthing cohort of 1,750 women (under two-step CC testing) 1 year prior to changing and 2,013 women (under one-step IADPSG testing) 1 year after changing to the IADPSG system. All diagnostic testing was performed by their hospital laboratory, and the same approach to GDM treatment, with the same thresholds for initiation of pharmacotherapy, was used in each time period.

Duran et al. (37) reported a trebling of the frequency of GDM with the change to IADPSG criteria, with a reduction in LGA babies and neonatal intensive care unit (NICU) admissions. The additional cost under IADPSG criteria was 3,753 Euro per 100 women. However, reduction in the frequency of cesarean section (CS) and NICU admission saved 20,090 Euro per 100 women. After accounting for other costs, the net saving was estimated at 14,358 Euro per 100 women. The rate of pharmacotherapy approximated 20% in both time periods, suggesting that the additional GDM cases were not (overall) "milder" than those previously detected and treated under the CC protocol.

In marked contrast, a similar pre/post study from Kaiser Permanente at Baldwin Park, Montebello, CA (38) involving 2,972 women under CC testing and 3,094 women under IADPSG testing showed an increase in GDM diagnoses from 17 to 27% with no reduction in LGA or CS across their hospital population. However, other important changes to diagnosis and therapy were introduced at the same time as the change to IADPSG diagnostic criteria. First, universal testing with HbA_{1c} was introduced into first trimester care, with $HbA_{1c} \geq 5.7\%$ used to define GDM. This change was associated with an increase in early GDM from 4 to 15%, explaining essentially all of the increased GDM frequency observed. Second, the temporal frequency of CS increased from the CC to the IADPSG period, both in GDM and non-GDM women, suggesting changes in underlying practice patterns. Third, the pattern of pharmacotherapy changed markedly, with glyburide usage in only 3% of GDM women in the CC period compared with 15% in the IADPSG period. At the same time, insulin therapy decreased from 36 to 14% among GDM women. In view of the multiple changes made, a clear conclusion regarding the IADPSG criteria alone is impossible in this cohort, but I suggest that these investigators actually identified a substantial population of women with more severe, likely prepregnancy hyperglycemia in the second "IADPSG" period. Since there are no clear data demonstrating the efficacy of standard GDM treatment in women with early (likely pre) pregnancy hyperglycemia, firm conclusions are not possible.

In my personal summary of the odyssey leading toward and the ongoing controversy leading onwards from the HAPO study and the IADPSG consensus, I would suggest that there is, in fact, no absolute "right" or "wrong" set of GDM diagnostic criteria. No set of thresholds will ever allow a dichotomous separation of the risk of adverse outcomes along an acknowledged continuum of hyperglycemia associated with a known continuum of risk. The IADPSG recommendations were clearly enunciated, and the process leading to their determination was well explained. They do identify a group of women at higher risk who are likely to benefit from current interventions for GDM. However, many questions remain, including the relative impact of treatment at various levels of glycemia, the degree to which glucose concentrations need to be "strictly normal," and the best approach to the increasingly common, poorly recognized, and inadequately understood situation of early/prepregnancy hyperglycemia.

ACTION

Both scientific insights and broad-scale epidemiologic and clinical trial data are arguably of limited use if they do not prompt effective changes in health care policy and practice. For this reason, I have chosen to deal specifically with efforts to change these pillars of clinical care, both through large-scale national and international collaborations and through local efforts at "real-world" implementation.

Almost every presentation or publication on diabetes deals with the current face of the "twin epidemics" of diabetes and obesity advancing on a global level (39). They have been termed a "slow-motion disaster" (40), and the dire predictions made even 10 years ago (41) now seem quaintly optimistic in light of adult diabetes prevalence rates >12% across many areas of the world. Of particular concern is the high prevalence of diabetes in low- and middle-income countries (LMICs), which are least able to afford the consequent personal, health care, and societal costs (42).

Hyperglycemia in pregnancy (HIP) represents an early, potentially sentinel part of the diabetes epidemic, with recent estimates suggesting that 21.4/127.1 million births each year across the world are affected by HIP and that >90% of cases occur in LMICs (43). Several international organizations have recognized the threat that HIP poses to otherwise improving maternal and neonatal outcomes. I have been involved with, and wish to highlight, the emerging role of the International Federation of Gynecology and Obstetrics (FIGO), which has recently published guidelines in this area (44) and is embarking on a global strategy of research, advocacy, and capacity building to address this serious health challenge. The FIGO approach is extremely pragmatic, recognizing that local resources and health care priorities, particularly in LMICs, dictate the extent to which testing for and treating HIP can be incorporated into routine maternity care. These guidelines offer the beginnings of a global strategic approach to HIP.

In addition to global strategy, local implementation is the lynchpin to effective health care delivery. I have been fortunate in collaborating with clinicians and health service planners in my local hospital and area, with the aim of enhancing and standardizing GDM care at the local level. My personal experience confirms that this requires both a sound theoretical framework—a logical process of identifying and addressing local barriers and enablers to changes in health care—and a large degree of hard work and persistence in pursuing changes to practice. Some of our recent publications in this area (45–47) outline the approach we have taken and the initial results obtained in the promotion of "best practice" in our local clinical environment. Involvement in this "coal face" domain of implementation research does not always bring high-profile or high-impact publications, but it remains essential if true and sustainable changes are to be achieved for the benefit of our patients and the broader community.

SYNTHESIS

In this article, as in my 2016 Norbert Freinkel Award lecture, I have attempted to draw together diverse elements across the translational spectrum from basic

biology, through clinical epidemiology and clinical trials, and into the area of implementation science.

My suggestions for the future advancement of our understanding and enhancement of the care of women with diabetes in care are several. In terms of basic knowledge, I believe that we need to deepen our understanding of pregnancy-related insulin resistance and the delicate counterbalancing effect of β-cell function, to better understand the similarities and distinct features of obesity and hyperglycemia as they affect pregnancy outcomes, and to investigate in detail the scope and optimal clinical approach to early pregnancy hyperglycemia.

In the clinical arena, I believe that we need to promote "what we know works" and champion the equitable availability of preconception and whole-of-life care for women with all forms of diabetes. As part of this process, we need to acknowledge and promote the evidence base for "standard" GDM diagnosis and care from the late second/early third trimester. We should expend less time and energy in debating the minutiae of diagnosis and devote more time and resources to the effective treatment of GDM.

In the area of implementation and action, I believe that all professionals dealing with diabetes in young women can make valuable contributions, primarily by addressing local barriers and enablers to ensure that care is optimal. It is important to influence local policy makers, reach a pragmatic local consensus, and commence formal local implementation. For those with sufficient energy and motivation, I urge you to actively collaborate on priority research questions such as those as outlined in this article.

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