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## NIH funds closed loop in pregnancy studies at Harvard, Mt. Sinai, Mayo Clinic, and Sansum; three-year, \$2.3 million grant - January 29, 2019

### Executive Highlights

- **NIH recently awarded a major \$2.3 million RO1 grant to Harvard, Mt. Sinai, Mayo Clinic, and Sansum to study closed loop in type 1 pregnancy.** This is the first US-based study of its kind. Our coverage below includes quotes from one of the study's PIs, Harvard's Dr. Eyal Dassau. Wow is this exciting and it has the late Dr. Lois Jovanic's legacy written *all* over it.
- **The first protocol, an observational study of insulin requirements and glucose levels using Dexcom G6 in type 1 pregnancy ("[LOIS-P](#)"), is already enrolling.** The investigators paid homage to Dr. Jovanovic with the acronym - using automated insulin delivery in pregnancy was always a dream of Dr. Jovanovic. There are also several closed loop protocols on tap over the next three years; the studies will leverage a modified version of Harvard's Zone MPC algorithm and the team's [iAPS mobile app](#).
- **This who's who of diabetes engineers and researchers could help make AID standard-of-care in pregnant women with type 1 diabetes** - a population with significant need and far-from-optimal outcomes. Cambridge's Dr. Helen Murphy and colleagues showed in a small sample ([NEJM 2016](#)) just how effective AID can be during one month of pregnancy, including during labor and the first 48 hours after delivery. The CONCEPTT study ([EASD 2017](#)) showed how even older CGM can make a difference in neonatal outcomes.

Harvard [announced](#) on Friday that it, along with researchers from Mt. Sinai, Mayo Clinic, and the Sansum Diabetes Research Institute, has received a prestigious RO1 grant from the NIH to evaluate a pregnancy-specific closed loop system, beginning with in-clinic studies and punctuated by an outpatient trial. These will be the first US studies of AID in type 1 pregnancy, and PI Dr. Eyal Dassau (Harvard) informed us that initial funding is \$2.3 million for three years. The other high-octane PIs are Drs. Carol Levy, Barak Rosenn, and Grenye O'Malley (Mt. Sinai), Dr. Yogish Kudva (Mayo Clinic), and Drs. Jordan Pinsker and Kristin Castorino (Sansum).

Phase one of the project - an observational study ("[LOIS-P](#)"; n=50) where women with type 1 are given a Dexcom G6 to track glucose levels through pregnancy and into the post-partum period - is already enrolling. Time-in-range (63-140 mg/dl), is the primary outcome, with other endpoints in the realm of insulin delivery, and maternal/fetal outcomes. It was fascinating to see the low end of the range and the high end and we were a bit surprised that the high end was so high (Kelly was coached through three pregnancies with Dr. Jovanovic as were legions of other women throughout the diabetes field - the goal for their high end was often much lower. Of course we understand for this study that this range was chosen by experts!) "LOIS-P" is an acronym for "Longitudinal Observation of Insulin Requirements and Sensor Use in Pregnancy," and was named after the legendary Dr. Jovanovic, who passed away [in September](#) and always dreamed of testing AID in pregnancy.

In addition to glucose and insulin trends through pregnancy, according to [ClinicalTrials.gov](#), insights gleaned from LOIS-P will be used to: (i) develop and refine algorithms for an AID system for pregnancy (i.e., insulin resistance and highly variable insulin requirements); (ii) serve as a control for concurrent AID protocols. Given this long list of applications, we're a bit surprised on one hand that the investigators are only enrolling 50 people though on the other, we know this will supply an extraordinary treasure trove of data (50 will also be considered a lot of women by many!) - Dr. Dassau said the group "would be open to extend the study if funding will support this and with the right regulatory support and approval."

"Several" closed loop protocols lined up, testing a version of Harvard's Zone MPC algorithm adapted for the insulin requirements and tighter glucose targets of pregnant women. The base Zone MPC algorithm is well studied - including [Dassau et al. 2015](#), [Dassau et al. 2017](#), and [Huyett et al. 2017](#) - which all demonstrated time in 70-180 mg/dl of 71%-79% and time <70 mg/dl of 1%-2.5%. The [iAPS \(interoperable Artificial Pancreas System\) mobile app](#), which notably runs on unlocked smartphones, will be used to deploy the controller and connected to pump/CGM. Dr. Dassau touted iAPS's flexibility (similar to UVA's DiAs platform), allowing both inpatient and outpatient studies with different level of supervision and monitoring, field updates, as well as (theoretically) the ability for participants to choose component pumps.

- **Dr. Dassau on the opportunity and feasibility of closed loop in pregnancy:** "The clinical glucose range for pregnant women is very different and much tighter than the acceptable 70-180 mg/dl range [for non-pregnant individuals]. The tight requirements and insulin resistance that is different each week of the pregnancy must be addressed in the core of the control algorithm. Automation can address this need to adjust insulin doses and avoid hyperglycemia, which is one of the main concerns. The use of predictive design will allow early action and as such will improve time-in-range and reduce glucose variability. As we have seen with current [closed loop systems], much improvement in time-in-range has been achieved in the last decade from the first modern closed loop studies to current systems. Such iterative improvement is predicted when we apply what we have learned integrated with available medical knowledge on the development of insulin resistance in pregnancy." We also note that "in real life," of course, many type 1s use tighter ranges than 70-180 mg/dl and we see that range as the "first range" approved for research and one that we believe may well be lower over time. This was the best range considered by many experts for research as the first step of standardization.
- **The last major news on closed loop in type 1 pregnancy front came in the form of a very positive, trailblazing [2016 NEJM publication from the Cambridge group](#).** In that study, sixteen pregnant women with type 1 diabetes completed four weeks of overnight closed-loop vs. four weeks of sensor-augmented pump (SAP) therapy; 14 choose to continue using the system 24/7 up to an additional 14.6 weeks, including during labor, delivery, and in the first 48 hours after delivery. Overnight time in a very tight target (63-140 mg/dl) was 75% during the four weeks of overnight closed-loop vs. 60% during the four weeks of SAP (p=0.002), with a lower average glucose (119 vs. 133 mg/dl) and no significant difference in hypoglycemia or insulin dose. During the continuation phase (median: 11.6 weeks), time in range was 69% with 24/7 closed-loop, including a mean blood glucose of 126 mg/dl. We expect this RO1 will build on this great work from Dr. Helen Murphy and colleagues.
  - **As Calgary's Dr. Jennifer Yamamoto [underscored at ATTD last year, type 1 pregnancy outcomes are far from acceptable.](#)** She highlighted a [2017 Diabetologia study](#) showing only 14% of pregnant women with type 1 diabetes and 37% of those with type 2 diabetes in England and Wales met the A1c target of <6.5%. Pregnancy preparation remains less than ideal, with high numbers of complications: Prevalence rates for congenital anomalies (46.2/1000 births for type 1, 34.6/1000 births for type 2) and neonatal death (8.1/1000 births for type 1, 11.4/1000 births for type 2) were unchanged as compared to 2002/2003. Making CGM standard of care in this population could go a long way too, as we learned in the JDRF-funded CONCEPTT study ([EASD 2017](#)).
- **According to its label, the MiniMed 670G has not been studied in pregnancy women.** We wonder how often it's being used off label in pregnancy and what outcomes look like! According to Dr. Irl Hirsch at [ACE 2018](#), it's not a great idea: "We're all in agreement that 670G is too conservative - once we get word that family planning is starting and the patient is off contraception, we go straight into manual mode." We also wonder if companies will do the AID studies to get their systems approved in this pregnancy population - obviously the pregnant type 1 population is a smaller market than others (e.g., pediatrics, Medicare), though AID could do a lot of good and save a lot of dangerous hypoglycemia.

-- by *Brian Levine, Adam Brown, and Kelly Close*