EFFECTS OF COVID-19 ON A LIFESTYLE INTERVENTION TRIAL: MODIFICATION OF STUDY VISITS AND METABOLIC EVALUATIONS

a research paper

by

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Abstract

Introduction: The onset of the COVID-19 pandemic in March 2020 resulted in a stay-at-home order that halted clinical research daily operations. Since 2019, Tufts Medical Center has been conducting a randomized clinical trial, Lifestyle Intervention in Preparation for Pregnancy (LIPP), which aims to break the obesity cycle by improving maternal health prior to pregnancy and subsequently fetal growth. The LIPP study visits include metabolic evaluations to measure body composition, oral glucose tolerance test (OGTT), resting metabolic rate, and VO2 max. The negative impact of COVID-19 on the study was the disruption of study visits.

Aim: To describe the modifications of LIPP study visits due to COVID-19 to ensure continuity of the metabolic evaluations.

Methods: Data was collected from study visit notes of LIPP participants. A timeline was created outlining the modifications made to the study protocol and the progression of the metabolic evaluations following the onset of COVID-19. We compared the study visit metabolic evaluation procedures before and after COVID-19 onset and reported the approaches taken to assure the progression of the study.

Results: Study participants required a series of study visits, which were halted from March to June 2020. Afterwards, the study was partially resumed where only limited metabolic evaluations could be performed (OGTT and body composition). Beginning in February 2021, the procedures were done completely for each study visit.

Conclusion: The modifications made to the protocol succeeded in ensuring the continuity of the LIPP study metabolic evaluations.

Introduction

Beginning in December 2019, a novel infectious disease, COVID-19, spread worldwide. COVID-19 is caused by a coronavirus strain known as SARS-CoV-2. The most prevalent symptoms of SARS-CoV-2 infection are fever and cough, but in severe cases, acute respiratory distress syndrome can develop. The virus is characterized by a rapid human-to-human transmission. Currently, global caseloads and mortality rates have reached nearly 500 million and over six million respectively [1]. Across the United States, over 28 million people have become infected [2], and more than 500,000 have died [2]. Due to the virus consequences and the impact of measures taken to contain the outbreak, it has led to a worldwide health crisis affecting all domains of clinical care and research. The stay-at-home order was a community reduction strategy used to contain the spread of COVID-19 in the United States.

The daily operations of clinical research were compromised. Several research activities had been stopped to curb the spread of COVID-19. Many researchers were forced to suspend research indefinitely or modify their protocols so as to continue remote research operations including recruitment, enrollment, intervention delivery, and follow-up of study participants. In order to continue clinical research during COVID-19, there was a need for finding “new” ways to safely conduct human studies. Our own research study, which relied on subjects’ access to clinical research areas and the performance of clinical tests, needed to be adapted in order to protect the welfare of our subjects and research staff. The transition to carrying out clinical trials under COVID restrictions has not been without its difficulties, particularly for studies that had been at an advanced stage.

The Lifestyle Intervention in Preparation for Pregnancy (LIPP) is a multicenter clinical research study examining the effects of healthy lifestyle interventions during pregnancy on the outcome of neonatal adiposity. The objective of the LIPP study is to enhance mothers' metabolic health and physical fitness for future pregnancies. Potential subjects are those who were either overweight or obese before conception, just delivered a baby, and are planing a next pregnancy. These subjects are recruited directly in the Mother and Infant Unit or in their first postpartum visit.

The LIPP study began recruiting in March 2017 at The Cleveland Clinic in Cleveland, OH. In November 2018 it also began recruiting research subjects at Tufts Medical Center in Boston, MA. Recruitment for the study has been completed in Cleveland, and is currently ongoing in Boston. Subjects are randomized into two cohorts: Intervention or Usual Care. The intervention participants meet with a lifestyle coach and routinely take part in visits intended to enhance lifestyle interventions like guided exercise sessions and healthy eating. The usual care participants are counseled on healthy lifestyle habits.

Each LIPP subject has scheduled visits done at Tufts Medical Center and Tufts University Human Nutrition Research Center on Aging (HNRCA).The LIPP study was negatively affected by the issuance of the stay-at-home order in March 2020, primarily due to its disruption to the study visit schedule. Visits could not be conducted, and it was unknown when, how, or if they could be resumed. The COVID-19 infection rate had fallen by June 2020, and the lifting of the stay-at-home order allowed the LIPP study visits to resume, albeit on a modified protocol. Modifications were made to the study protocol in order to accommodate these limited study visits. The modified study visits continued until February 2021, when the previously established (prior to Covid-19) protocol was resumed. The aim of this paper is to report on the modifications made to the LIPP study protocol due to the COVID-19 pandemic.

Methods

Methodology for this report consisted of reviewing study visit records and comparing the procedures performed before and during Covid. The modifications made to the protocol were reported and compared to the previously existing protocol prior to Covid restrictions. Tufts Medical Center Institutional Review Board (IRB) is the central IRB for the LIPP and has approved the study protocols. All participants have provided written informed consent prior to participation.

Results

Prior to the pandemic, a LIPP study visit was composed of several maternal metabolic assessments. Study visits were performed by study staff upon appointment at the Clinical and Translational Research Center at Tufts Medical Center and the HNRCA at Tufts University. The LIPP protocol was published in *Contemporary Clinical Trials* in 2020 [3]. The maternal metabolic assessments are briefly described. Maternal metabolic testing is done at baseline (approximately 3 months postpartum) and then at 6, 9, 15, and 21 months postpartum (Figure 1). In the subsequent pregnancy (i.e. LIPP pregnancy), assessments are made at early gestation (12-16 weeks) and late pregnancy (32-36 weeks) (Figure 1). Metabolic assessments include body composition, resting energy expenditure, exercise capacity, insulin sensitivity and cell function, as well as a quality of life questionnaire. Exercise capacity test is omitted at the pregnancy visits.

Body Composition. Anthropometric measurements of the subject's height and weight, as well as hip and waist circumferences, were recorded. Body composition was measured utilizing the Bod Pod (whole body air plethysmography). The Bod Pod is a device that measures the subject's weight and volume to establish body density and calculate body fat percentage, fat mass, and fat free mass..

Resting Energy Expenditure. Indirect calorimetry was employed to measure the rate and route of substrate oxidation (carbohydrates and fat) in the fasting state.

Exercise Capacity (VO2max). An incremental treadmill test was done to assess maximum oxygen consumption.

Insulin Sensitivity: An oral glucose tolerance test (OGTT) was performed to evaluate insulin sensitivity. Following an overnight fast, blood samples are taken at -10, 0, 30, 60, 90, 120 and 180 minutes after glucose ingestion.

Quality of Life Questionnaire: A questionnaire is used to evaluate each subject's quality of life in regards to their health.

Our clinical research strategies during COVID-19 included the integration of additional safety measures for visits, truncated visits, and an alternate method of data collection (Table 1).

Since in-person observations were important to the study, subjects underwent COVID-19 screening (such as symptoms or reported contact with potentially infected individuals) 48 hours in advance and also upon arrival at the appointment. Stringent hygiene procedures were followed and visits were limited in scope and duration. All study visits were moved to the Tufts Medical Center research clinic since the HNRCA building was closed indefinitely. Research staff wore additional personal protective equipment. Figure 2 describes the timeline for the adjustments necessary to continue the LIPP study visits despite COVID-19.

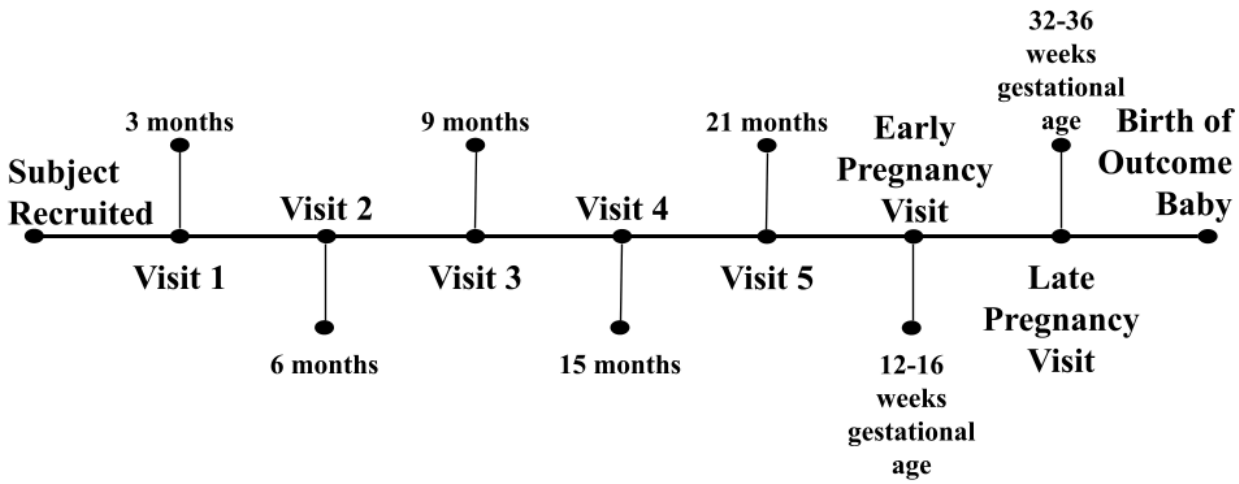

Figure 1: LIPP timeline for study visits.

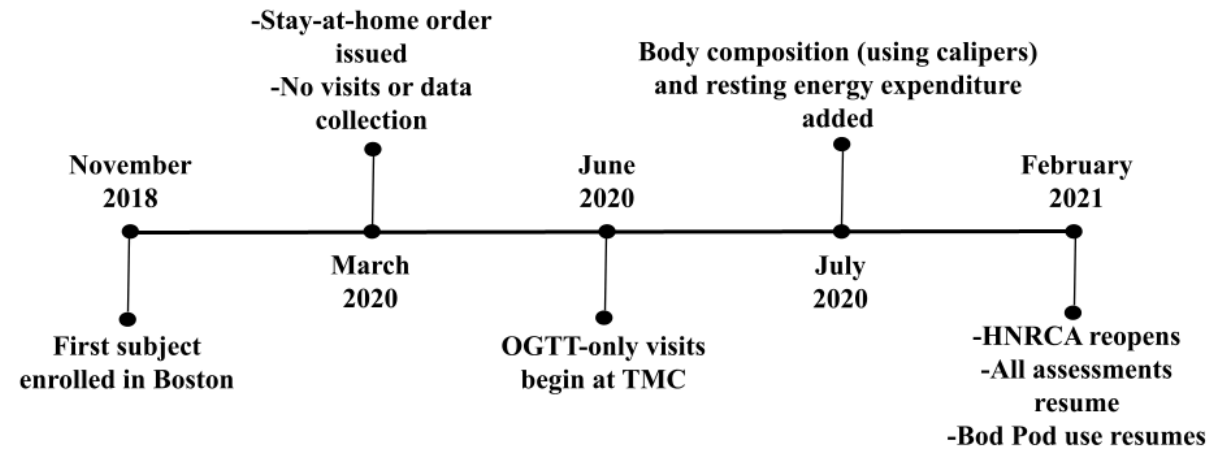

Figure 2: LIPP study timeline modifications during and after the stay-at-home order. The order was lifted in January 2021. The previously-used protocol was fully resumed in February 2021.

Maternal Assessments	*Original LIPP Protocol*	*Protocol Modifications due to Covid*
Visit Scheduling	Visits scheduled one hour apart	Visits scheduled two hours apart in order to allow time for additional cleaning and disinfection procedures
Study Visit Appointment	Participant came to LIPP study visit at the scheduled date	Participant had to complete a covid screening test 48 hr prior to study visit
Personal Protective Equipment (PPE)	PPE included a lab coat and gloves for clinical staff	Also needed to wear safety goggles and mask
Visit Location	Visits conducted at HNRCA and Tufts Medical Center	Visits only could be conducted at Tufts Medical Center
Metabolic Tests	Visit tests comprised of body composition, VO2max, OGTT, indirect calorimetry, and quality of life questionnaire	OGTT only (June-July 2020) OGTT, indirect calorimetry, and body composition only (July 2020-February 2021)
Body Composition	Body composition taken using Bod Pod	Body composition estimated using calipers (June 2020-February 2021)

Table 1: Modifications made to the LIPP previous protocol during the COVID-19 pandemic.

Discussion

Before Covid, each subject enrolled in Boston would have their metabolic assessments completed at both the Tufts University HNRCA and at Tufts Medical Center. However, when Covid restrictions were loosed and resuming study visits in some format became a possibility, HNRCA had not yet reopened. Having only Tufts Medical Center available to conduct study visits, it was decided that study visits would resume there in June 2020. The only assessment that could be done at Tufts during that period was the OGTT since the equipment for indirect calorimetry and body composition were located at the HNRCA. Although these visits would be very limited in scope, conducting them would require a number of modifications in order to keep staff and subjects safe, and also to comply with the Covid restrictions that remained in effect. Since Tufts Medical Center is a hospital; study visits would need to be conducted in compliance with Covid regulations that remained in effect at the hospital, city, state, and federal levels. Therefore, the LIPP protocol was modified to include several additional protective measures. Firstly, subjects would need to pass a Covid symptom/exposure phone screening 48 hours prior to their appointment, and then again upon arrival at their appointment. LIPP staff were required to wear safety goggles during the visit, and both staff and subjects were required to wear masks in order to protect themselves and others from Covid. Whereas before Covid study visits were scheduled at one-hour intervals, they were now scheduled at two-hour intervals in order to allow additional time to disinfect instruments and clinical areas between visits. With these modifications to the LIPP protocol, OGTT-only visits began in June 2020 and continued until July 2020, when assessments for indirect calorimetry and body composition were able to be added back into the visits. The indirect calorimetry instrumentation was relocated from the HNRCA to the research clinic at Tufts Medical Center. Since the Bod Pod was located at HNRCA, it remained unavailable for use for the body composition assessment. An additional protocol modification was made which allowed for measures of body composition using calipers and an anthropometric formula instead of the Bod Pod. With the reopening of HNRCA in February 2021, all metabolic assessments were resumed, as well as the use of the Bod Pod for body composition.

The Covid pandemic has negatively impacted clinical research involving human subjects at all levels. While a number of studies were halted indefinitely, others, such as trials for cancer and other serious conditions, could not be halted or even temporarily paused. Like the LIPP study, these studies continued through the pandemic using any modifications required to do so. While modifications pertaining to preventing the spread of Covid have been universal, other modifications have varied widely. Other common study protocol modifications have included virtual and phone appointments/visits, alternative methods of delivering study drugs and materials to subjects (such as by mail), and various methods of reducing the frequency and duration of close physical contact with subjects and other staff [4]. Clearly, perfect solutions to the impacts of Covid on human studies have been few and far between, but flexible and oftentimes creative modifications have allowed many studies, like LIPP, to persevere through the pandemic.

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