Tommy's National Reproductive Health Biobank: A Virtual Networked Resource

INTRODUCTION

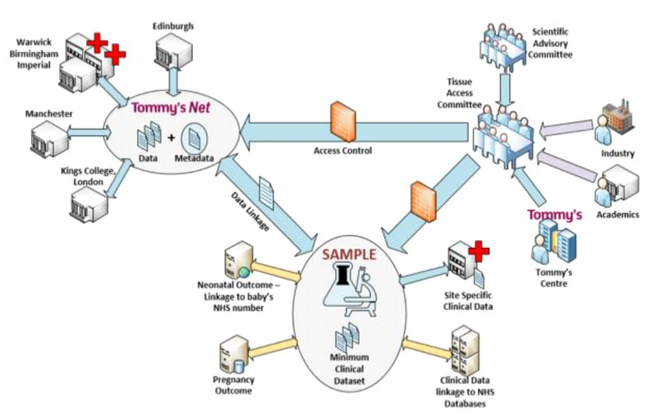
Reproductive health permeates every aspect of human society. Disorders of reproductive health and pregnancy are some of the most common with up to 10% of couples experiencing subfertility, 31% of pregnancies ending in miscarriage and pregnancy related conditions being the most common reason for hospital admission worldwide[1-3]. Despite the prevalence large knowledge gaps remain pervasive and common conditions are poorly understood. Research in the area has been hampered by tissue collection on the basis of retrospective reproductive outcome rather then prospective. The Tommy's National Reproductive Health Biobank (TNRHB) was formed in 2018 to try and bridge this gap.

TNHRB STRUCTURE

The TNHRB is a virtual biobank combining a prospective reproductive outcomes registry with six existing biobanks across Tommy's funded research centres. These operate under a single governance structure, with material and data sharing agreements and a single-consent model. This allows collection of samples from mother, father and baby, using expert-designed standard operating procedures, ensuring collection of high-quality samples. Sample collections are held at each site and linked by bespoke tissue tracking software developed by Warwick University's Institute for Digital Health (IDH).

AIMS AND OBJECTIVES

- Accelerate research in reproductive health by providing high quality samples and data efficiently
- To link samples to metadata, clinical data, pregnancy outcome data and neonatal outcome data
- To review sample access applications within 2 weeks of receipt.
- To work closely with industry partners



SAMPLES AND DATA

- Dedicated midwives, funded by Tommy's the charity , approach participants for consent and sample donation at each of the research centres.
- Consent is granular, allowing participants the choice to agree or disagree to donate the different types of samples during there clinical care at the centres
- Samples can be collected prospectively following successful application to access samples from the biobank.
- Permission to re-contact for future research studies and trials
- Provision of samples and data incur a charge to help cost recovery.
- Sample collection is ongoing; to date we have **2500 samples from 373 participants** (total number of consented participants 925, not all participants donate a sample at time of consent). A summary of sample type and core dataset is outlined below:

Biospecimens (can be processed as required, this table shows frozen samples unless stated otherwise)

Maternal Biospecimen	No.	Paternal Biospecimen	No.	Baby Biospecimen (up to 1 week old)	No.
Blood: EDTA Plasma	1	Blood: EDTA Plasma	0	Urine	0
Blood: EDTA Serum	0	Blood: EDTA Serum	0	Saliva	0
Blood: EDTA for DNA	130	Blood: EDTA for DNA	0	Buccal Swab	0
Blood Germline DNA	66	Urine	0	Hair from back of scalp	0
Amniotic Fluid	0	Buccal Swab	0	Meconium	21
Breast Milk	8				
Urine	94				
Placenta & Membranes	FFPE 154 Frozen 297				
Cord	83				
Cord blood	83				
Buccal Swab	0				
Vaginal Swab	255				
Endometrium	755				
Myometrium	467				
Omentum	0				
Subcutaneous fat	0				

Exemplar Project Specific Sample Cohort	
Sample Number	354
Sample Type	Endometrial tissue
Median Age (Range)	36 (26-47)
Reproductive Phenotype	
Recurrent Implantation Failure	172
Recurrent Miscarriage	142
Ectopic	17
Endometriosis	13
Other	18
Unspecified	51

Tommy's National Reproductive Health Biobank Minimal Clinical Dataset
Demographics *(Mother and Father)*
Age
Ethnicity
Consent – answer of "yes" or "no" to each statement of the consent form is recorded
Obstetrics *(Mother)*
Number of Pregnancies 24+0-36+6 weeks
Number of Pregnancies 14+0 – 23+ 6 weeks
Number of Pregnancies 37+0 weeks or later
Expected Delivery Date
Onset of Labour- uterine contractions resulting in progressive cervical effacement and dilatation
If onset of labour is not spontaneous reasons for induction or pre labour Caesarean section predefined list includes fetal growth restriction, gestational diabetes, pre-eclampsia, other complications
Cerclage
When Sampled *(Mother)*
Age at registration
Pregnant
Booking BMI
Smoker predefined list
Name of medications taken Free text field
Medication status- started preconception, since conception, and whether continuing or stopped.
Outcome *(Mother)*
Outcome of pregnancy miscarriage (early, late), live born, still birth, molar pregnancy etc.
Mode of Delivery vaginal (assisted, unassisted), caesarean section, breach, etc
Indication for operative delivery either/ both fetal, maternal problems.
Birth weight
Birth weight customized centile
Pregnancy complication, none, hypertension, preeclampsia, Eclampsia, Small gestational Age (SGA), Fetal growth restriction (FGR), haemolysis elevated liver enzymes and low platelet count (HELLP)

ENGAGEMENT

- Tommysbiobank.org website is closely linked to the Tommy's Charity website, to encourage participant engagement
- Tommy's Charity have produced videos to help advertise the biobank, these are available to view on You Tube, Facebook, twitter and LinkedIN
- Tommy's Charity website has a page dedicated to the biobank
- The biobank is registered on various platforms; Biosample HUB, Biobanking.com, Tissue Solutions and UKCRC Tissue Directory to increase visibility
- We encourage those attending conferences to promote the biobank by including a slide at the end of their presentation.
- PPI groups are consulted on the content of consent material

PROJECTS SUPPORTED

SAMPLE ACCESS

Sample and data access is obtained following:

1. A consultation with the clinicians, providing expert advice and guidance on project feasibility and suitability.
2. Full project application
3. Review by the TNRHB Tissue access committee comprised of experts in reproductive health; midwives and patient representatives
4. Payment of agreed cost recovery charges. This includes a project set up fee, application fee and charge per sample

Number of Projects Supported to date

Year	Number of general enquiries received	Number of applications received	Number of applications approved	Number of samples released
2019	4	9	9	670
2020	6	6	6	280

Types of Projects Supported to date	No.
Early detection of infections by developing accurate point of care tests	2
Looking at the microbiome, immune cells and underlying mechanisms of endometrium in miscarriage	5
Tocolytic studies- mechanisms and drug discovery	2
Importance of nutrition in improving pregnancy outcomes	1
Determining optimum transfer window for successful embryo implantation	1
Research in to placental function in pregnancy complications.	4

INDUSTRY COLLABORATION

The biobank is proud to be working with the pharmaceutical industry:

Ferring is an international pharmaceutical company; a leader in reproductive medicine and maternal health. The company is working with researchers at Warwick University to develop a new drug to inhibit uterine contractions as a tocolytic treatment for preterm birth. The biobank will collect and supply myometrium tissue.

As part of the CooperSurgical family, CooperGenomics works in partnership with the CooperSurgical fertility companies towards the common goal of improving patient outcomes and IVF success. Successful pregnancy depends on the synchronous processes of healthy embryo development and endometrial preparation. It has been shown that up to 40% of infertile patients seeking treatment through assisted reproductive technologies display abnormal endometrial preparation and show a displaced window of implantation (WOI), the brief timespan in the menstrual cycle during which the endometrium is receptive to an implanting embryo. A shift in the WOI may lead to mistimed embryo transfer, lower implantation rates and reduced reproductive success. Accurate determination of endometrial receptivity based on molecular markers allows IVF clinicians the opportunity to adjust the embryo transfer timelines to accommodate displacement in the window of implantation. Evidence suggests that accurate assessment of receptive preparation in a given cycle can be leveraged in subsequent cycles to define an optimal transfer window. This study aims to analyse inter-cycle consistency of WOI displacement to determine the utility of endometrial receptivity testing. The biobank is providing endometrial tissue for this study.

CASE STUDY:

THE CHRONIC ENDOMETRITIS AND RECURRENT MISCARRIAGE (CERM) TRIAL

CERM Chronic Endometritis and Recurrent Miscarriage

INTRODUCTION

Recurrent miscarriage affects 5% of couples trying to conceive. It carries significant morbidity. In the majority of couples, no clear cause is identified making treatment difficult. One purported cause is chronic endometritis (CE). However, to date no randomised controlled trial has assessed this and the mechanism remains poorly understood.

OBJECTIVE

To assess the effect of doxycycline on livebirth rates in women suffering from RM and CE. Secondarily to assess the mechanism by which CE causes miscarriage.

METHODS

Prospective double-blinded placebo controlled randomised adaptive designed trial.

BIOBANK COLLABORATION

Biobank tie-in has allowed the generation of a combined mechanistic/clinical trial. Diagnostic endometrial samples are collected under the auspices of the biobank allowing researcher application to support a diverse range of mechanistic studies across a range of centre collaborations. Tying in with the RCT allows samples tied to the appropriate clinical phenotype, treatment group and clinical outcome whilst also allowing mechanistic work to build upon new discoveries across fields. To our knowledge this is a novel integration of a biobank within a clinical RCT. To facilitate this integration novel SOPs were created to facilitate specific trial collection procedures.

RESULTS TO DATE

Despite the impact of Covid-19, the CERM trial has progressed apace and to date generated 374 samples from 86 patients. This has allowed initial work to understand the constitutive pattern of expression of CD138 a marker of plasma cells used in the diagnosis of CE. Current work across two sites is assessing the characteristics of the endometrium within CE and that of the endometrial microbiome associated with CE.

BUILDING COLLABORATION

The use of the biobank with its overarching material and data sharing agreements has led to the development of new collaborations within the mechanistic work of the trial. The development of a collaboration with Imperial College London facilitated by the biobank has allowed specialist microbiome work to be understood. A further collaborative development with the University of Oxford is currently being established. This collaboration will extend the biobank beyond Tommy's funded research units.

IMPACT IN THE FIELD

Despite the trial only having 3-months of recruitment to date. Mechanistic work within the trial driven by the biobank has been presented in the European Society of Human Reproduction and Embryology: 'The importance of timing in detection of asymptomatic CD138 diagnosed chronic endometritis.' Additionally, several peer-reviewed publications are now in development including the novel integrative biobank design.

ACKNOWLEDGEMENTS

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