Pregnancy | Mobile Healthcare | Personalized Medicine

Special Articles on Advanced Technologies

Collaboration Projects

Joint Research Achievements for Prevention and Early Detection of Disease during Pregnancy —Clarifying Patterns of Change in Lifelogs and Body Substances That Show Signs of Disease—

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Utilizing the NTT DOCOMO Group's mobile healthcare platform to collect and analyze body substances of pregnant women and their daily lifelogs, NTT DOCOMO has clarified patterns of change in lifelogs and specific body substances that indicate signs of pregnancy-related diseases for the first time. This enables the risk of onset of pregnancy-related diseases to be evaluated based on the constitution, physical condition and lifestyle of the pregnant woman. Then, the lifestyle of the pregnant woman can be improved to promote the health of the mother and child. This research was conducted jointly with Tohoku University Tohoku Medical Megabank Organization (Professors Masao Nagasaki, Junichi Sugawara, et al.).

1. Introduction

NTT DOCOMO is working to resolve social issues through its services with the goal of creating value through collaborative creation with various partners. As these social issues are also found in the medical and healthcare fields, NTT DOCOMO is also promoting R&D to solve problems in various stages of life such as lifestyle-related diseases and hence contribute to the realization of healthy and fulfilling longevity, especially through prevention of diseases such as hypertensive disorders and diabetes during pregnancy, a major event for women and their families, and for their children who are starting out in life.

Pregnancy-related diseases (hypertensive disorders of pregnancy, gestational diabetes, preterm birth, fetal growth retardation, etc.) affect the health of mothers and infants throughout pregnancy and postpartum. Approximately 20% of pregnant women are affected with these diseases in Japan. Many of these diseases are caused by complex interactions of

genetic and environmental factors. Therefore, comprehensive analysis of genetic factors and keeping track of changes in environmental factors are crucial to understanding the cause of these diseases. Until now, many research institutions and local governments have obtained environmental information using questionnaires, but this has been limited in its frequency of acquisition and accuracy due to self-reported questionnaires only being acquired about once every six months. In addition, research that comprehensively tracks changes in body substances*1 in the blood and urine samples of pregnant women weekly or more frequently and research that comprehensively analyzes differences in the lifelogs*2 and body substances between pregnant women who became ill and those who gave birth without getting ill, have not been performed.

To address these issues, this research aimed to frequently collect the daily lifelogs (blood pressure, heart rate, room temperature, body temperature, body weight, physical activity, physical condition, sleep status, fetal movement, meal content, medication content, etc.) and body substances (DeoxyriboNucleic Acid (DNA)*3, RiboNucleic Acid (RNA)*4, metabolites and bacterial flora*5, etc) of pregnant women as objective numeric values, and analyze this data to understand the changes in lifelogs and physiological conditions to establish personalized prevention and early detection methods of diseases that occur during pregnancy [1] [2]. As a result, we built one of the world's largest research databases on pregnant women, and were able to identify patterns of change in lifelogs and body substances that indicate signs of disease.

This article describes an overview of this research, details of its findings, the expected value of it and the outlook for the future.

This research was conducted jointly with Tohoku University Tohoku Medical Megabank Organization (Professors Masao Nagasaki, Junichi Sugawara, et al., hereinafter referred to as ToMMo).

2. Overview of the Research

2.1 Flow of the Research

NTT DOCOMO and ToMMo began joint research for the prevention and early detection of pregnancy-related diseases on November 19, 2014 [3]. From September 14, 2015 to November 15, 2016, we recruited pregnant women at the Tohoku University Hospital for this research, under the name "maternity log study." 302 pregnant women were recruited and gave their written informed consent [4]. Also, from November 15, 2016, we began integrated analysis of lifelogs and body substances obtained from participants [4]. We concluded the joint research on March 31, 2019 after producing a range of findings which are discussed later.

2.2 The Roles of NTT DOCOMO and ToMMo

The lifelogs of pregnant women were collected daily using the mobile healthcare platform operated by the NTT DOCOMO Group (**Figure 1** (1)). Collection of biological samples such as blood, urine and dental specimens of pregnant women was carried out at Tohoku University Hospital adjacent to ToMMo (Fig. 1 (2)). NTT DOCOMO and ToMMo collaborated to convert information about body substances included in these biological samples into data (Fig. 1 (3)). This enabled us to build a comprehensive database capturing the lifestyles and

*1 Body substances: Substances in blood, urine and dental specimens, etc., from which information about DNA, RNA, metabolites and bacterial flora can be obtained.

*2 Lifelog: A record reflecting the health status and lifestyle habits of an individual, including blood pressure, heart rate, room temperature, body temperature, body weight, physical activity, physical condition, sleeping conditions, fetal movement, diet and medication details, etc.

*3 DNA: A substance carrying genetic information in an organism and consisting of deoxyribose and phosphoric acid, and four types of nucleobases: adenine, guanine, cytosine, and thymine.

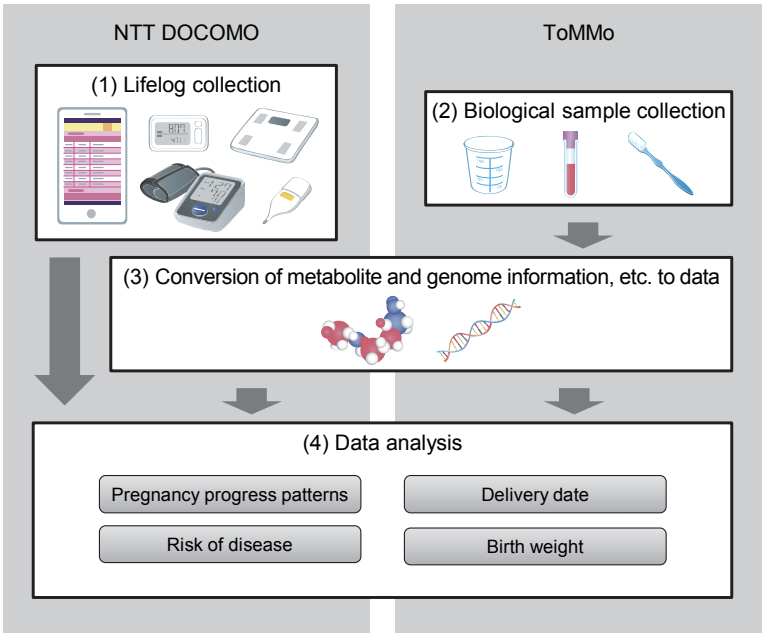

Figure 1 The roles of NTT DOCOMO and ToMMo

physical conditions of the pregnant women during pregnancy. After that, NTT DOCOMO and ToMMo combined DOCOMO's big data analysis technologies it has fostered through analysis of various time series data and AI technologies such as machine learning*6 with ToMMo's information analysis technologies such as genome*7 and life & information science technology to jointly analyze the data (Fig. 1 (4)).

3. The Data Platform

3.1 Lifelogs

As shown in **Table 1**, the daily lifelogs of pregnant women were collected using various devices and applications. The registration rate, which indicates the degree to which lifelogs were measured and input, was approximately 80% or more for most items during pregnancy, which was an amount of data sufficient to comprehensively analyze the daily activities and physical conditions of the pregnant women (**Figure 2**). In the end, the collected lifelogs contained a total of approximately 6 million items of data [4] [5].

3.2 Body Substances

To collect biological samples containing body substances such as blood and urine samples, blood and dental specimens were collected twice during pregnancy and once after birth. In addition, urine samples were collected each routine antenatal visit,

*4 RNA: A substance transcribed using DNA as a template, and composed of ribose and phosphoric acid, and four types of nucleobases: adenine, guanine, cytosine, and uracil. While DNA primarily plays the role of accumulating and preserving information in the nucleus, RNA is responsible for temporary processing of that information.

*5 Bacterial flora: The community of bacteria growing in a certain environment.

*6 Machine learning: A technology that enables a computer to learn useful judgment standards through statistical processing from sample data.

Table 1 List of collected lifelog items

Item	Device or application used		Details of measurement	No. of measurements per day	Measurement, input timing	Time required
Body temperature		Electronic thermometer for women	Basal body temperature	Once	After getting up, lying down	Approximately 10 seconds
Body weight		Weight and body composition meter	Body weight	Once	On principle, within 1 hour of getting up (after using the toilet)	Approximately 4 seconds
Blood pressure		Upper arm blood pressure monitor	Blood pressure, heart rate	Twice	On principle, within 1 hour of getting up (after using the toilet) Before bedtime (after using the toilet)	Approximately 1 minute
Physical activity		Activity monitor	No. of steps, calories consumed	Carried always	–	–
Sleep		Pre-Mama health app (Developed by NTT DOCOMO Research Laboratories)	Bedtime/getup time Quality of sleep No. of wake ups during sleep	Once	Optional	Approximately 10 seconds
Nausea			Time taken feeling nauseous No. of times dry vomiting, vomiting	Once	Optional	Approximately 10 seconds
Uterine contractions, etc.			Uterine contractions, bowel movements Level of pain in each area Palpitations	Once	Optional	Approximately 10 seconds
Fetal movement			Time taken to feel 10 fetal movements	Once	Time slot when fetal movements feel strongest *Measured after the 24th week of pregnancy	Approximately 3 to 10 minutes

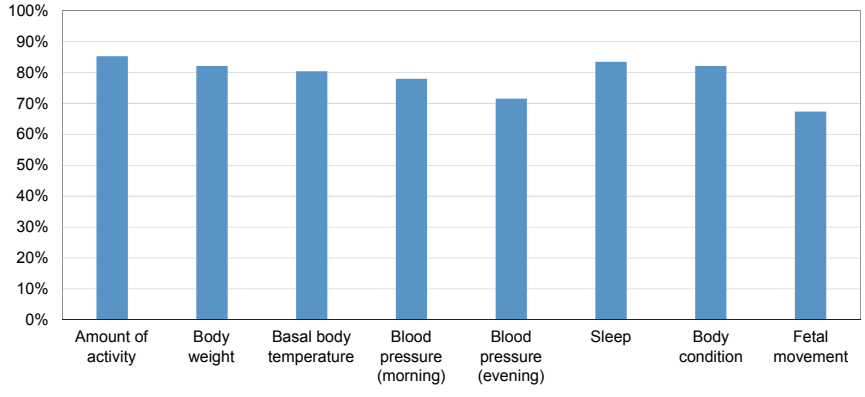

Figure 2 Lifelog registration rates

*7 Genome: All the genetic information in all the base sequences of the DNA constituting an organism's chromosomes.

which finally resulted in approximately 8,000 samples collected [3] [5]. As shown in **Table 2**, analysis of the information on the body substances in these specimens resulted in the accumulation of large amounts of data on multiple layers such as genes and metabolites. This enabled understanding of processes that lead to symptoms of disease and changes in physical condition due to the influences of genetic and environmental factors.

4. Findings of the Research

Integrated and chronological analysis of the above lifelogs and body substances revealed many new findings on pregnancy-related diseases. This chapter describes three of the main research findings.

4.1 Determining Patterns of Change in Lifelogs as Signs of Pregnancy-related Diseases

The database we built enabled a general understanding of the dynamic changes of various lifelog items as pregnancy progresses. For example, as pregnancy progresses, **Figure 3** shows increasing frequency of uterine contractions and increasing weight, while basal body temperature and daily physical activity decrease. Significant differences

Table 2 Body substance information collected from specimens

Biological sample collection	Body substance information
Blood	Millions of genetic mutations
Blood	Tens of thousands of RNA expression levels (multiple time points)
Blood, urine	Hundreds of metabolite levels (multiple time points)
Saliva, plaque	Composition ratio of hundreds of bacterial flora (multiple time points)

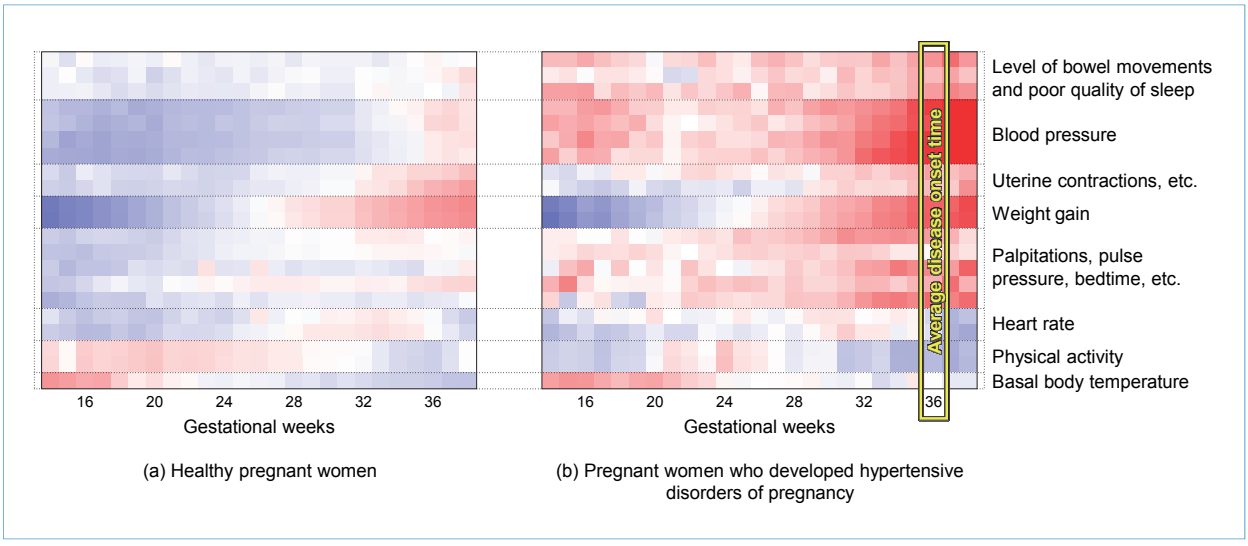

Figure 3 Patterns of lifelog change during pregnancy (red is high, blue is low)

were also found in the fluctuation patterns of various lifelogs between healthy pregnant women and pregnant women who developed pregnancy-related diseases. For example, the results clarified that pregnant women who developed hypertensive disorders of pregnancy tended to have higher home blood pressure from an earlier stage than healthy pregnant women, and that their quality of sleep was poor throughout their pregnancy. Please note that we plan to publish the details in academic journals.

These results enable AI detection of the onset of disease from lifelog fluctuations, suggestions for lifestyle improvements for pregnant women who are likely to develop disease, and enable early examination and treatment by obstetricians or other doctors, and therefore hold promise for personalized prevention and medical treatment to prevent the onset of disease.

4.2 Identification of Metabolites Useful for Predicting Delivery Date

Examination of the relationship between the delivery date in cases in which the child was born at full term and related changes in metabolites in urine and blood samples revealed that there was a characteristic change in specific metabolite concentrations as the delivery date approached. For example, a metabolite was identified in the urine samples that increased in concentration continuously from approximately two weeks prior to delivery until the delivery date (**Figure 4**). Using several combinations of these metabolite concentration changes makes it possible to predict the delivery date with AI, which will be useful to pregnant women and their families for planning for the date of delivery. This also enables medical institutions to prepare for delivery in advance, which should contribute to safer births. We plan to report the details of delivery date prediction at the Society

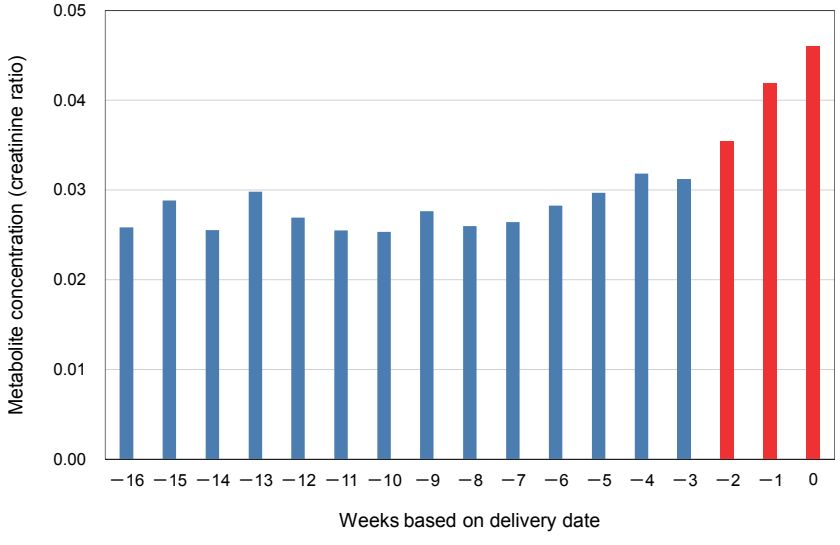

Figure 4 Changes in concentration of metabolite A in urine samples up to delivery date (red: characteristic changes)

for Reproductive Investigation (SRI) 2020 [6], the world's largest international conference on perinatal medicine.

4.3 Identification of Genetic Mutations Useful for Birth Weight Prediction

In recent years, low birth weight infants are increasing in Japan. To investigate the genetic association, we searched for genomic mutations in pregnant women related to birth weight, and identified genetic mutations specifically related to birth weight. Each occurrence of this gene mutation was found to reduce birth weight by an average of approximately 400 to 500 g (**Figure 5**). These results make it possible to know in advance genetically whether there is a risk of an infant being born with low weight, and thus hold the promise of realizing personalized prevention and medical care that enables early diagnosis and treatment by an obstetrician or other physician if there is a high risk of low birth weight.

5. Conclusion

Regarding research conducted by NTT DOCOMO and ToMMo aiming to establish methods of prevention and early detection of illnesses in pregnant women, this article has described an overview of the research we conducted, the big data we accumulated, our research findings, and the outlook for the future. As part of its "+d®*8" initiative to collaborate with partners to create new value, NTT DOCOMO will work to further verify the results of this joint research and put them to practical use to achieve a society in which more pregnant women can give birth safely without being affected by illness (**Figure 6**). We would like to extend the early detection and prevention of illnesses beyond pregnant women and contribute to extending the healthy life expectancy*9 of citizens.

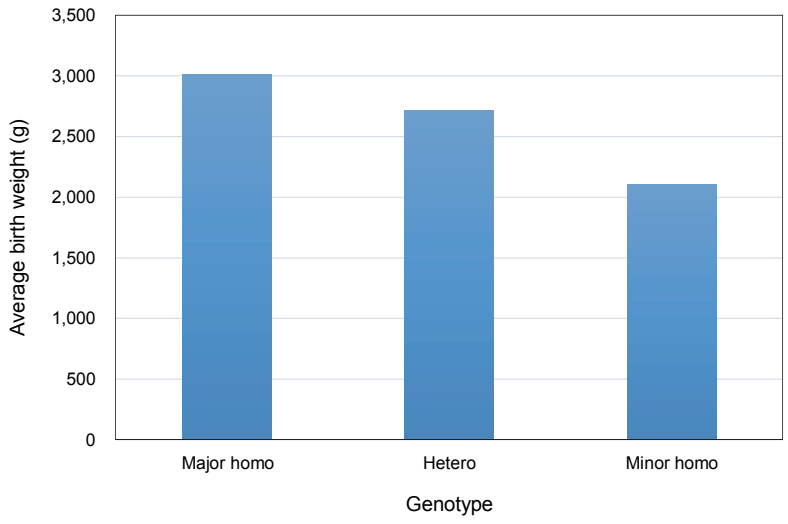

Figure 5 The relationship between genetic mutation B and birth weight

*8 +d®: A NTT DOCOMO medium-term initiative to move forward with its partner companies to create added value in various business areas. A trademark or registered trademark of NTT DOCOMO, INC.

*9 Healthy life expectancy: The expected period of good health in daily life.

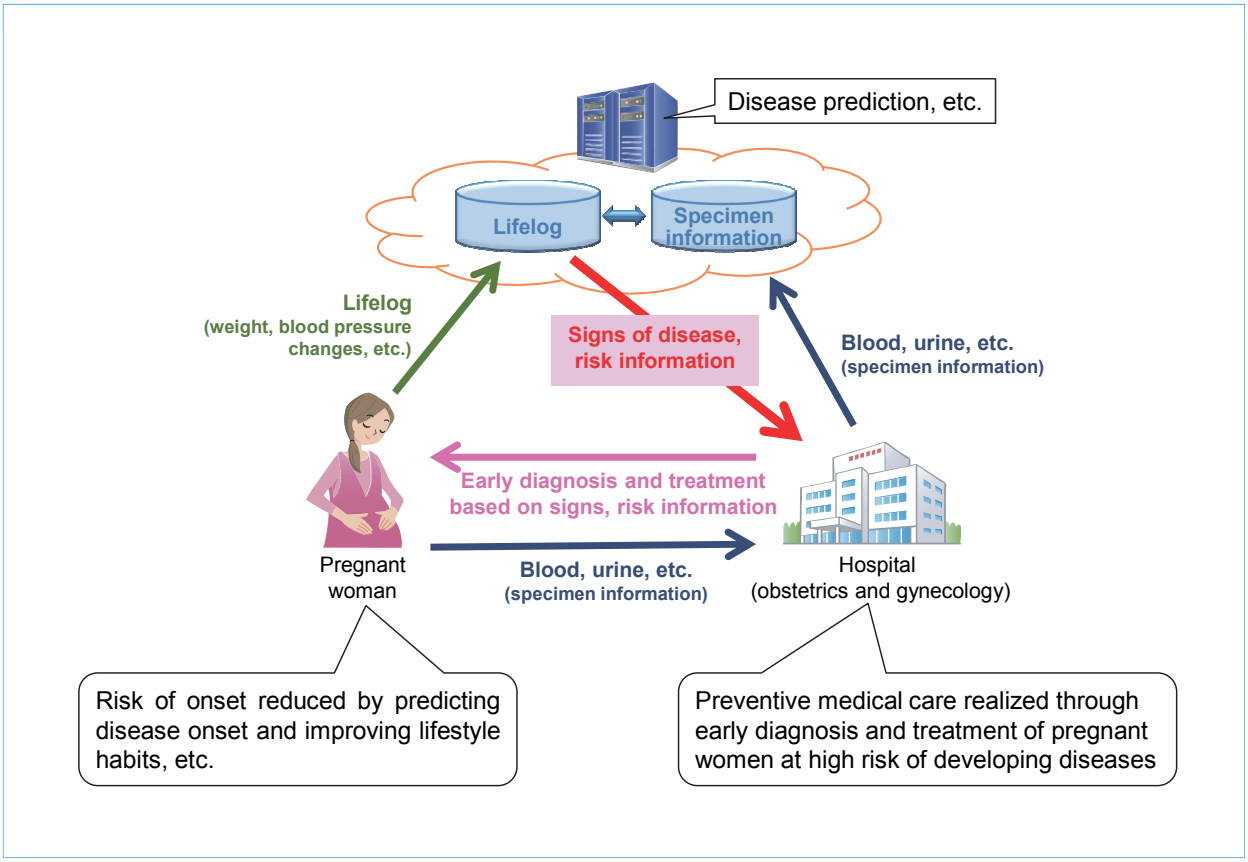

Figure 6 Examples of social implementation of research results

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