Advances in Clinical and Translational Research
Volume 1
Article ID: 100009

Research Article

A Comparison Study on Safety and Efficacy of Maternal Abdominal-Lead Fetal ECG Under Regulatory Science

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Received: June 10, 2018; **Accepted**: July 14, 2018; **Published**: July 21, 2018

Abstract

In current clinical practice, there has been no clinical trial of fetal electrocardiography (fECG) from middle trimester. In this study, we investigated the safety and validated the efficacy of maternal abdominal-lead fetal electrocardiography machine (IRIS™) to be able to estimate beat by beat fetal heart rates from 24 weeks gestation.

Twenty-three singleton pregnant women (24~42 weeks) were recruited to simultaneously record 20 minutes' abdominal lead (12 leads) fECG with direct-lead fECG (scalp electrodes) and doppler signal based CTG signals. Subjects were divided into three groups (Group 1: 37~42 weeks of pregnancy (n=7), Group 2: 32~36 weeks (n=6), and Group 3: 24~31 weeks (n=10)). Direct lead fECG were collected from only Group 3.

The clinical safety of long-term measurement with the abdominal-lead fECG device (IRIS™) was positively validated. Beat by beat fetal heart rates measurement (over 18000 beats) showed a strong correlation ($r>0.9$; $p=0.02$) with the same from direct-lead fECG. Bland–Altman plots showed good agreements of IRIS™ (mean differences were -0.6(+8.69 upper and -9.86 lower limits) and +0.3 beats per minutes (bpm) (+0.38 upper and -0.24 lower limits) with direct lead fECG and doppler CTG devices respectively.

The abdominal lead fECG device (IRIS™) was validated for its clinical safety for long term measurement as well as for beat by beat fetal heart rate estimation in comparison with direct lead fECG and doppler CTG machines. This device has the potential to become an important clinical tool for monitoring fetal cardiac functions from as early as 24 weeks of gestation.

Keywords: fetal electrocardiography (fECG), abdominal lead fECG, clinical trial

1. Introduction

Since the 1960s Ultrasonic Doppler fetal heartbeat monitoring (CTG) and direct-lead electrocardiograms with scalp electrodes have been used for monitoring fetal well-being in clinical practice. However, there have many reports of false alarms from CTG and sometimes abnormal variability in FHR may not necessarily represent the fetus in distress [1,2].

Because of the limitations, alternative to those previous methods have been explored since 1990s [3-5]. Non-invasive maternal abdominal-lead fetal ECG methods have increasing been popular because of convenience and non-invasiveness. But extraction of fetal ECG from abdominal signals is challenging because of very low signal to noise ration and high non-stationarities [6]. That is why non-invasive fetal ECG device have not been implemented in clinical settings for fetal monitoring purpose [7,8]. Recently Monica Healthcare fetal ECG (AN24) was used to acquire abdominal-lead fetal ECG from only 37 weeks and after.

We have been working on the development of a maternal abdominal-lead fetal electrocardiograph since 2004 [6]. However, before the fetal ECG can be used for clinical fetal monitoring, a system clinical trial with the medical device regulatory authority (for examples, FDA in the US, PMDA (Pharmaceuticals and Medical Devices Agency in Japan)) is needed. According to PMDA, patient safety and efficacy in terms of measurement precision in clinical settings are needed to get the device approved as a fetal ECG based heart rate monitor from 24 weeks.

Therefore, in this study, we evaluated i) the safety of a maternal abdominal-lead fetal electrocardiograph, and ii) compared with control devices by simultaneously recording.

2. Materials and Methods

2.1 Subjects

In this study, 23 pregnant women from 24 weeks to 41 weeks of pregnancy were recruited from the prenatal check-up clinic at the Tohoku University Hospital between April and December 2013. The study protocol was approved by Human Research Ethics Committee of Tohoku University Graduate School of Medicine. The trial was registered on AT138 with Ministry of Health in Japan. All participants gave informed consents. Subjects were divided into three groups, namely, Group1 (7 cases from 37 weeks to 41 weeks of pregnancy), Group 2 (6 cases from 32~36 weeks), Group 3 (10 cases from 24~31 weeks) (Figure1, Table1).

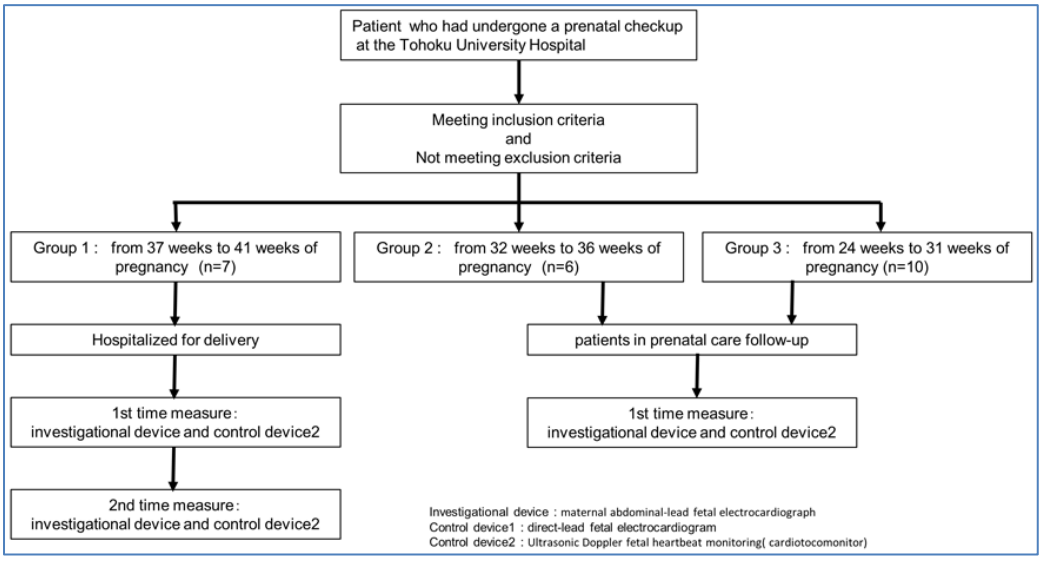


Figure 1: Subjects of this trial, divided into three groups and measured on this flow chart. Patients in group 1 were measured two times whereas patients in Group 2 and 3 were measured only once

Table 1: Background of cases and measurement conditions

Group 1: 7 cases from 37 weeks to 41 weeks of pregnancy									
No.	**Age (years)**	**Gestational weeks**	**Para**	**Gravida**	**EFBW (g)**	**BMI (kg/m²)**	**Discontinued**	**Incidence of adverse events**	**Incidence of failures**
1	36	39w 0d	2	2	2738	19.3	Yes	No	—
2	29	38w 5d	0	0	3131	30.4	No	No	Yes
3	29	39w 1d	3	2	2838	23.3	No	No	Yes
4	43	41w 0d	3	0	3251	26.8	No	Yes	No
5	34	38w 6d	0	0	2948	23.9	No	No	No
6	36	40w 4d	0	0	2996	28.6	Yes*	Yes	No
7	27	41w 0d	0	0	3203	31.8	No	Yes	No
Group 2: 6 cases from 32 weeks to 36 weeks of pregnancy									
No.	**Age (years)**	**Gestational weeks**	**Para**	**Gravida**	**EFBW (g)**	**BMI (kg/m²)**	**Discontinued**	**Incidence of adverse events**	**Incidence of failures**
1	35	34w 4d	4	2	2076	24.9	No	No	Yes
2	39	32w 4d	1	0	2072	29.2	No	No	No
3	41	35w 4d	2	2	2462	21.7	No	No	No
4	28	33w 2d	0	0	2135	18.6	No	No	No
5	43	36w 6d	3	0	2461	26	No	No	No
6	36	35w 5d	0	0	2364	27.8	No	No	No
Group 3: 10 cases from 24 weeks to 31 weeks of pregnancy									
No.	**Age (years)**	**Gestational weeks**	**Para**	**Gravida**	**EFBW (g)**	**BMI (kg/m²)**	**Discontinued**	**Incidence of adverse events**	**Incidence of failures**
1	24	27w 1d	1	1	1080	22.1	Yes	No	—
2	29	28w 3d	0	0	1283	24.5	No	No	Yes
3	41	28w 3d	0	0	1298	26.1	No	No	Yes
4	39	29w 0d	0	0	1522	23.4	No	No	Yes
5	26	27w 4d	2	2	1116	26.2	No	No	Yes
6	32	26w 5d	4	2	953	19.1	No	No	No
7	22	24w 3d	1	0	583	21.1	No	No	No
8	35	29w 5d	0	0	1594	22.5	No	No	No
9	32	29w 2d	0	0	1455	20.7	No	No	No
10	38	25w 3d	1	1	916	20	No	No	Yes

*No6 in group 1 was accomplished 1st time measure, but 2nd time measure was discontinued.

EFBW: Estimated Fetal Body Weight**;** BMI: Body Mass Index

Patients, who were hospitalized for delivery, were included in group 1. Fetal heart rate data captured from the investigational device (abdominal-lead method) were compared with two control devices (direct-lead method (control device 1), ultrasound Doppler method (control device 2)).

Patients in Group 2 and 3 were recruited from outpatient prenatal care check-up unit of Tohoku University Hospital. Fetal heart rate data from the investigational device were compared with the control device 2 (ultrasound Doppler method) only.

Following inclusion and exclusion criteria were considered in this study

2.2 Inclusion criteria

- Signed on written Consent form
- Age 20 years or older
- Gestational age in the range of 24~42 weeks
- Prenatal check-up results are urine protein (+) or less, urine sugar (+) or less
- Blood pressure less than 140 mmHg/ 90 mmHg
- Negative indirect Coombs test results

2.3 Exclusion criteria

- Patients who were diagnosed as having an infectious disease (hepatitis B, hepatitis C, HIV, syphilis, HTLV-1, rubella, or chlamydia) at the time of registration based on the result of an infection test performed during the current pregnancy
- Diagnosed with multiple pregnancy, abnormal pregnancy, pregnancy with an obstetric complication (e.g., gestational diabetes, gestational hypertension, uterine fibroids, and cervical cancer)
- Diagnosed with a serious medical disease or a mental illness, severe anemia (Hb 8.0 g/dl or less),
- Those who had participated in the same group in this study
- Scheduled for Caesarean section
- Others determined to be inappropriate by an investigator or a co-investigator

2.4 Fetal ECG measurement

Maternal abdominal-lead fetal electrocardiograms were recorded in the ordinary bedside setting without special equipment such as shielded room for this measurement. Figure 2 explains the actual procedure in 4 steps. *Step 1:* Cover a bed with noise elimination sheet, and let the subject lie on it in the supine position or semi-Fowler's position. *Step 2:* Attach a total of 12 electrodes to the maternal abdomen, right subclavian, and lumbar regions of the subject simultaneously with an ultrasound transducer for the ultrasonic Doppler signal measurement. *Step 3:* Perform measurement on the subject resting in bed. *Step 4:* Remove electrode seals after measurement. (Figure 2). Fetal ECG signals were extracted by a method as explained in the patent (PCT/JP2005/023601, PCT/JP2006/316386) and IRIS is a trademark registered by Atom Medical Co for this device.

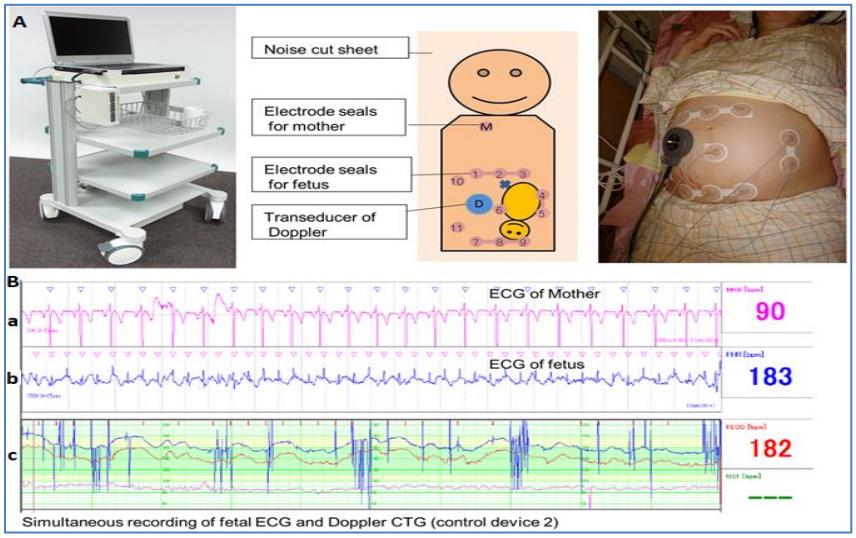


Figure 2: (A) Abdominal-lead fetal electrocardiogram and its screen **(B)** Fetal ECG Screen **(a)** upper panel shows maternal ECG **(b)** middle panel (blue line) shows fetal ECG, and **(c)** lower panel shows fetal and maternal heart rate (the blue line is fetal heart rate of fetal ECG, the red line is fetal heart rate from control device 2, the pink line is maternal heart rate)

2.5 Endpoint

2.5.1 Safety and efficacy endpoints

- Incidence of adverse events
- Completion rate (cases in which measurements were completed with no serious deviation and assessable data were available, at least one measurement was performed)
- Evaluation of device failures (rates of occurrence of failures for the investigational and control devices, such as failure to analysis and detection of electrodes)
- Evaluation of the usability (if there was any difference in time required for setting up the electrodes and the device by midwives)

2.5.2 Comparative evaluation of fetal heart rates

- Comparative evaluation of abdominal-lead fetal electrocardiographic heartbeat signals (investigational device) and direct-lead fetal electrocardiographic heartbeat signals (control device 1)
- Comparative evaluation of the investigational device and ultrasonic Doppler heartbeat signals (control device 2) (Figure 3)

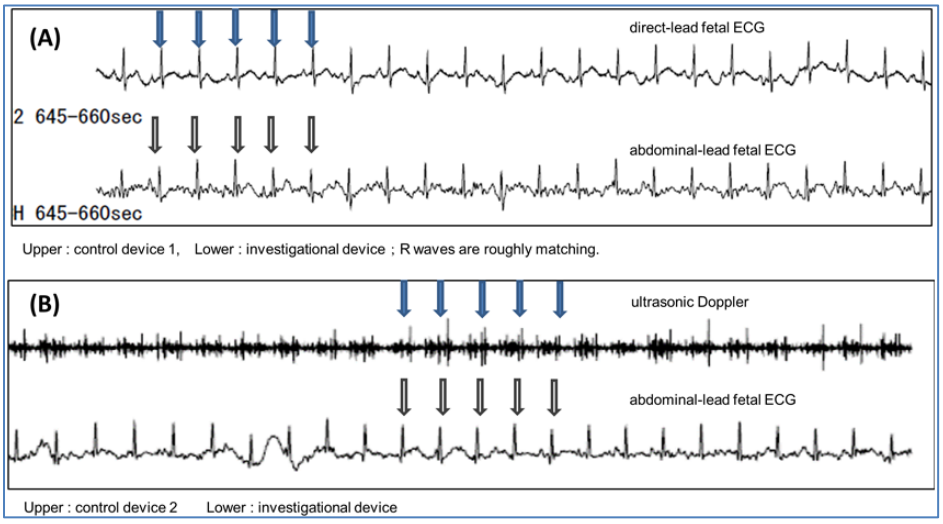


Figure 3: (A) Comparison of the abdominal-lead fECG heartbeat signals (investigational device) and direct-lead fetal ECG heartbeat signals (control device 1) **(B)** Comparison of the abdominal-lead fECG heartbeat signals (investigational device) and ultrasonic Doppler heartbeat signals (control device 2)

2.6 Analysis techniques

Comparative analyses were performed when simultaneous measurements with the control device were completed with no serious deviation and fetal heartbeat data (at least two consecutive segments (15 sec per segment)). Pearson's correlation coefficient and Bland-Altman plots were used to compare the fetal heart rate data from the investigational device and control devices. Since there was a time lag occurred in fetal heart rates from control device 2 due to autocorrelation processing, comparisons were made with the investigational device data with and without averaging process prior to analysis.

In the averaging process, inter-device discrepancies were noticed because the investigational device acquires data depending on the R-wave recognition, while control device 2 acquires data every 0.25-second time window. Therefore, the moving average was computed for the data within a 3.75-second interval, and the time axis was shifted by 3 seconds to adjust the delay time of the control device 2 (3-4 seconds).

3. Results

3.1 Measurement outcomes

In group 1 (control device 1), 5 underwent successful measurements and 2 discontinued of 7 registered cases; in group 1 (control device 2), 6 underwent successful measurements and 1 discontinued of 7 registered cases. Discontinued cases did not meet the inclusion criteria. In group 2, all of 6 registered cases underwent successful measurements. In group 3, 9 underwent successful measurements and 1 discontinued of 10 registered cases due to the faultiness in a part of electrodes. Therefore, assessable data on the primary endpoint were available from 6 cases in group 1, 5 cases in group 2, and 5 cases in group 3. Cases suitable for comparative evaluation of fetal heart rates were 4 cases in group 1, 2 cases in group 2, and 3 cases in group 3.

3.1.1 Safety and efficacy evaluation (Table 1)

3.1.1.1 Incidence of adverse events: Adverse events occurred in group 1 who underwent Cesarean section (3/6 patients, 50%) and had non-reassuring fetal status (3/6 patients, 50%). No adverse events were noticed in group 2 nor in group 3. The overall incidence rate of adverse event was 14.3%.

3.1.1.2 Successful completion rates: Two types of completion rates were computed. The completion rate type1 ((the number of cases with assessable data on the primary endpoint)/ (the number of cases that underwent measurements) × 100 (%)) were found to be 5/6 (83.3%), 5/6 (83.3%), and 5/9 (55.6%) for group 1,2 and 3 respectively. On the other hand, the completion rate type 2 ((the number of cases with assessable data on the primary endpoint)/(the number of cases that underwent measurements without peripheral equipment faultiness) × 100 (%)) were found to be 5/6 (83.3%), 5/5 (100%) and 4/4 (100%) for group 1,2 and 3 respectively.

3.1.1.3 Evaluation of failure rates: The failure rates were calculated as a ratio of the number of failures occurred over the total number of measurements (i.e., Ratio = (the number of failures) / (the number of measurements) × 100 (%)). The failure rates of Investigational device were found to be 2/11 (18.2%), 1/6 (16.7%) and 5/9 (55.6%) for group 1,2, and 3 respectively. The overall failure ratio was 8/26 (30.8%) for all groups together. Control devices 1 and 2 caused no failures in this study. Specifically, types of failures were either due to analysis program stopped in the middle of analysis (1 each in groups 1 and 2) or measurement/recording stopped working for some electrodes (4 in group 3) or loose port connections (1 each in groups 1 and 3).

3.1.1.4 Evaluation of the usability: Set up or removal of electrodes took less than 3 minutes to complete after proper training to midwives or nurses conducting the experiments.

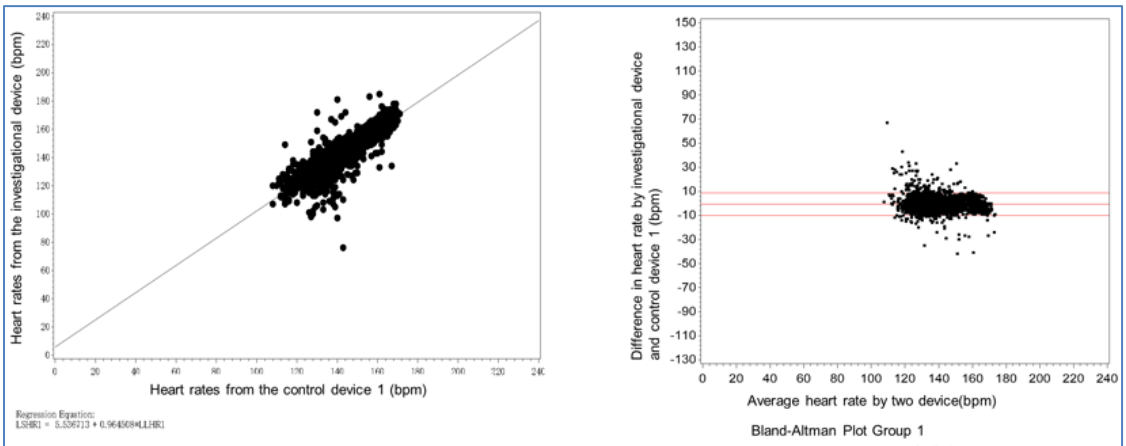
3.1.2 Comparative evaluation of estimation of fetal heart rates

3.1.2.1 Comparative evaluations of abdominal-lead fetal electrocardiographic heartbeat signals (investigational device) and direct-lead fetal electrocardiographic heartbeat signals (control device 1) (Group 1 only) (Figure 4A) were made for 4 cases. The overall correlation coefficient was found to be 0.925 ($p<0.01$) (n=6276 beats). The correlation coefficients (r) of individual cases were shown to be 0.848 for case No. 2 (n=2046 beats), 0.505 for case No.4, (n=899 beats), 0.833 for case No.5 (n=1697 beats) and 0.643 for case No.7 (n=1634 beats).

Heart rates from the investigational device and control device 1 showed moderate to high correlation (r=0.505~0.848). Heart rate error analysis (Bland-Altman Plot) showed overall mean difference: -0.6 (n=6276) which is less than 1 bpm. Individually the mean differences were -0.6 for No.2, -0.5 for No.4, -0.6 for No.5 and -0.6 for No.7 respectively. The results show that investigational device underestimates the fetal heart rates by less than 1 bpm.

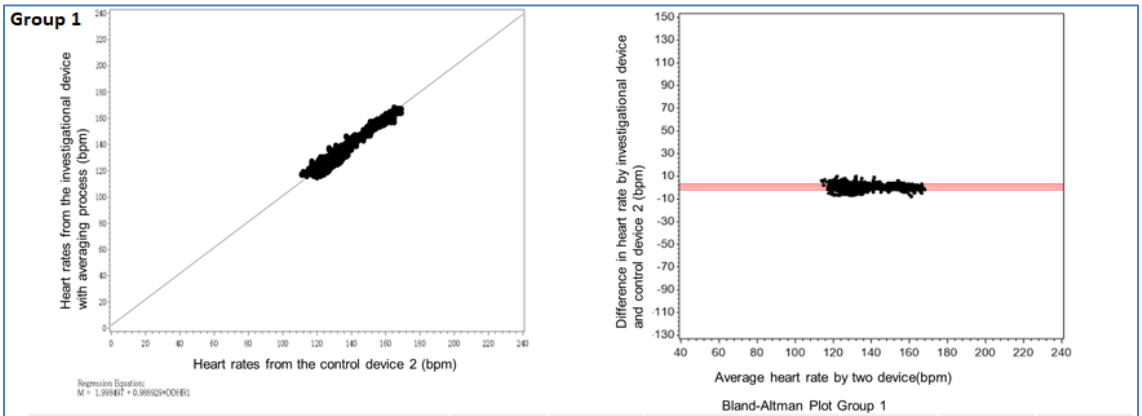
3.1.2.2 Comparative evaluations of estimation of fetal heart rates with ultrasonic Doppler heartbeat signals (control device 2) (Figure 4B1-4B3) were made for 6, 2 and 3 cases in group 1, 2 and 3 respectively. The overall

correlation coefficient (r) of Group 1 was found to be 0.995 (n=18485). The r of individual cases was 0.957 for No.2, 0.994 for No.3, 0.949 for No.4, 0.949 for No.5, 0.975 for No.6, and 0.909 for No.7.



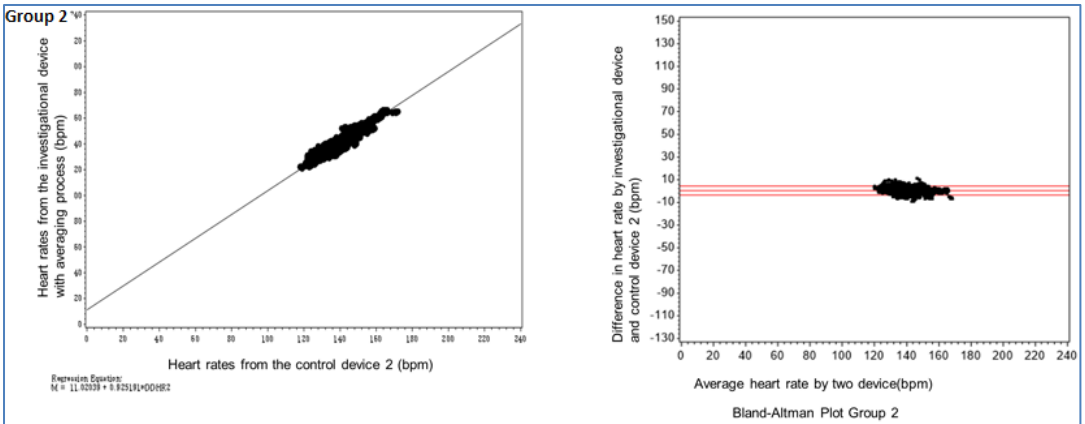
Group 1		No.2	No.4	No.5	No.7	Total
Data number of investigational device		2046	899	1697	1634	6276
Data number of control device 1		2046	898	1697	1634	6275
Correlation coefficient		0.848	0.505	0.833	0.643	0.925
Heart rate error analysis	Mean difference (bpm)	-0.6	-0.5	-0.6	-0.6	-0.6
	Lower limit of confidence difference(bpm)	-0.8	-0.82	-0.81	-0.81	-0.7
	Upper limit of confidence difference(bpm)	-0.47	-0.21	-0.3	-0.35	-0.47

Figure 4A: Evaluation of the equivalence of two devices. Abdominal-lead fECG heartbeat signals (investigational device) and direct-lead fetal ECG heartbeat signals (control device 1) in total group 1



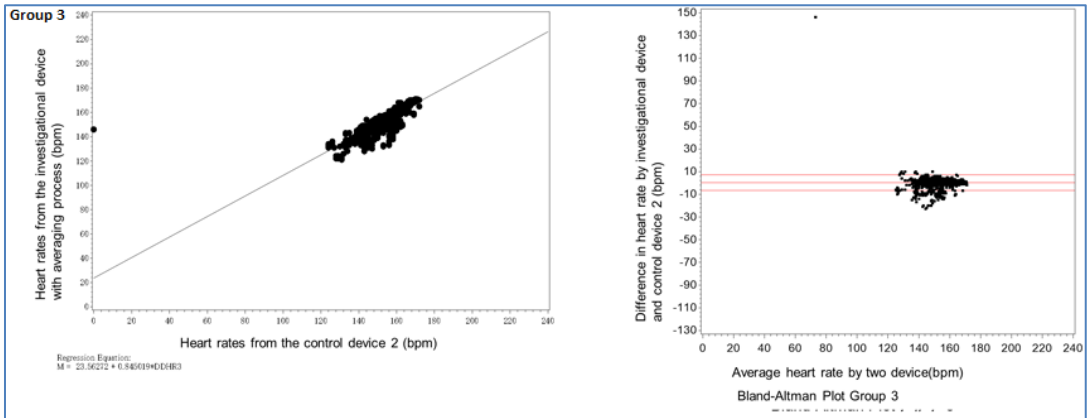
Group 1（with averaging process）		No.2	No.3	No.4	No.5	No.6	No.7	total
Data number of investigational device		4396	1065	4093	771	4472	3688	18485
Data number of control device 2		4396	1065	4093	771	4472	3688	18485
Correlation coefficient		0.957	0.944	0.949	0.949	0.975	0.909	0.995
Heart rate error analysis	Mean difference (bpm)	0.5	0.4	0.4	0.8	0.5	0.4	0.5
	Lower limit of confidence difference(bpm)	0.5	0.35	0.42	0.67	0.46	0.37	0.47
	Upper limit of confidence difference(bpm)	0.56	0.49	0.48	0.84	0.52	0.48	0.5

Figure 4B1: Evaluation of the equivalence of two devices. Investigational device and ultrasonic Doppler heartbeat signals (control device 2), with averaging process in Group 1



Group 2 (with averaging process)		No.3	No.6	total
Data number of investigational device		3470	2475	5945
Data number of control device 2		3470	2475	5945
Correlation coefficient		0.968	0.98	0.973
Heart rate error analysis	Mean difference (bpm)	0.3	0.6	0.4
	Lower limit of confidence difference(bpm)	0.25	0.52	0.38
	Upper limit of confidence difference(bpm)	0.39	0.63	0.47

Figure 4B2: Evaluation of the equivalence of two devices. Investigational device and ultrasonic Doppler heartbeat signals (control device 2), with averaging process in Group 2



Group 3 (with averaging process)		No.7	No.9	No.10	total
Data number of investigational device		4113	778	3688	8579
Data number of control device 2		4113	778	3688	8579
Correlation coefficient		0.415	0.856	0.863	0.904
Heart rate error analysis	Mean difference (bpm)	0.7	0.1	0	0.3
	Lower limite of confidence difference(bpm)	0.52	-0.14	-0.09	0.24
	Upper limite of confidence difference(bpm)	0.77	0.27	0.07	0.38

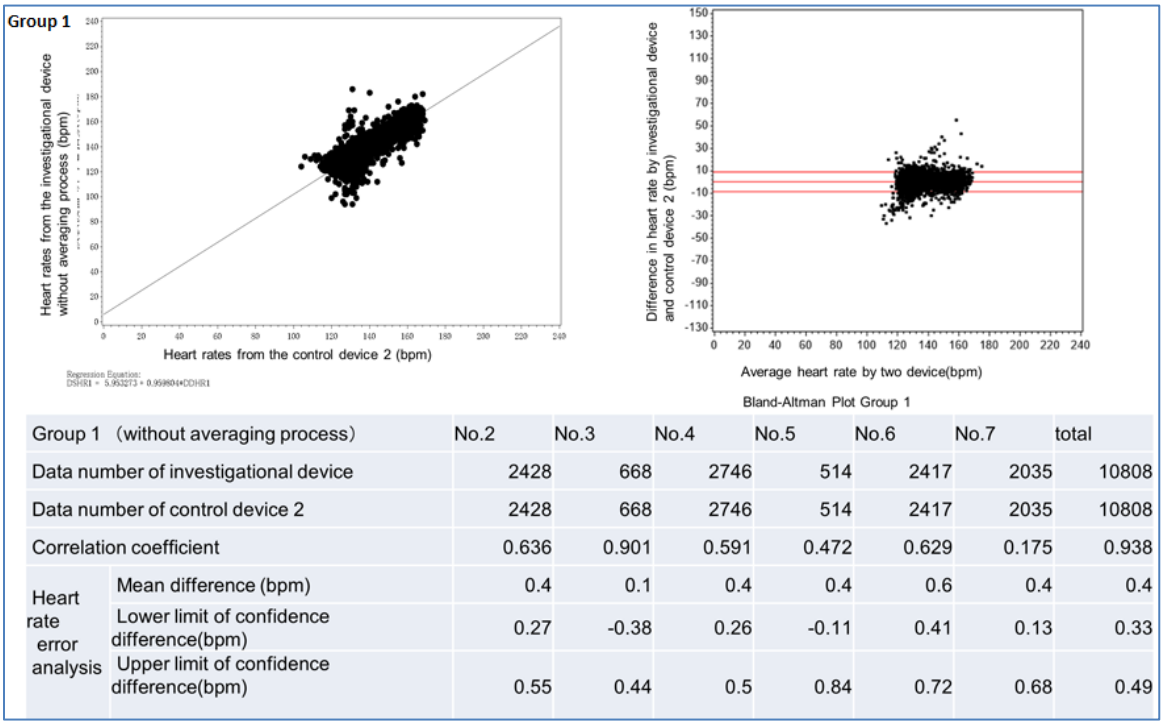
Figure 4B3: Evaluation of the equivalence of two devices. Investigational device and ultrasonic Doppler heartbeat signals (control device 2), with averaging process in Group 3

Similarly, the same of Group 2 was 0.973 (n=5945) for all subjects and 0.968 for No.3 and 0.980 for No.6 individually. The overall r of Group 3 was 0.904 (n=8579) and individually 0.415 for No.7, 0.856 for No.9, and 0.863 for No.10.

In summary, correlation was found to be high in all groups. Particularly, the highest correction coefficient (r>0.995) was found in the group of 37 weeks or more. On the other hand, the lowest correlation was seen in the younger groups. Heart rate error analysis (Bland-Altman Plot) showed the mean difference 0.5 (n=18485) for Group 1 as a whole and 0.5 for No.2, 0.4 for No.3, 0.4 for No.4, 0.8 for No.5, 0.5 for No.6 and 0.4 for No.7 respectively. As for Group 2, the mean differences were 0.4 (n=5945) for overall and 0.3 for No.3 and 0.6 for No.6 individually. Similarly, for Group 3 the same were 0.3 (n=8579) for overall and 0.7 for No.7, 0.1 for No.9 and -0.0 for No.10 individually.

Mean difference and addition error was less than 1 bpm indicating that the investigational device tends to overestimate fetal heart rate a little bit.

Figure 4C1-4C3 summarizes the results for comparison of fetal heart rate data obtained without subjecting the investigational device data to averaging process. The correlation coefficients of Group 1 were found to be 0.937 (n=10808) for all subjects as a group and 0.631 for No.2, 0.897 for No.3, 0.580 for No.4, 0.466 for No.5, 0.622 for No.6, and 0.161 for No.7 respectively. Similarly, the same of Group 2 were 0.739 (n=3642) for all subjects as a group and 0.703 for No.3 and 0.776 for No.6. Finally, the same of Group 3 were 0.713 (n=5536) as a whole and 0.255 for No.7,0.297 for No.9, 0.438 for No.10 individually.

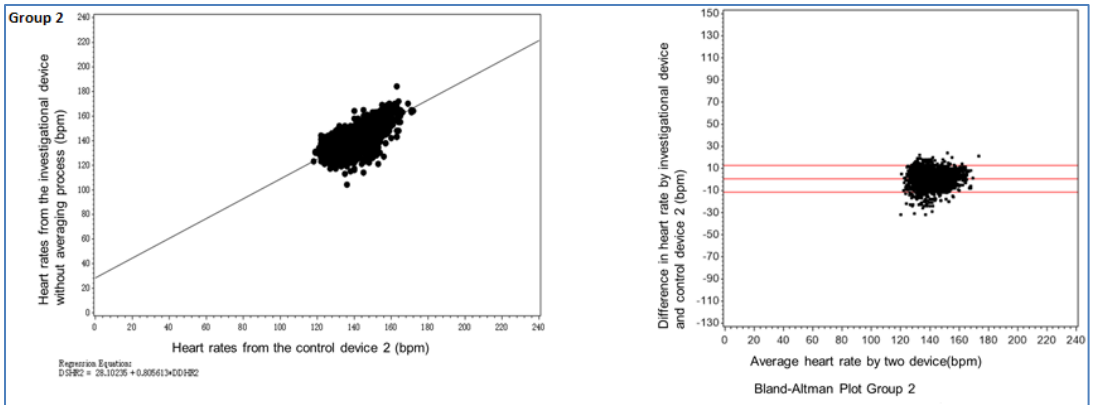


Group 1 (without averaging process)		No.2	No.3	No.4	No.5	No.6	No.7	total
Data number of investigational device		2428	668	2746	514	2417	2035	10808
Data number of control device 2		2428	668	2746	514	2417	2035	10808
Correlation coefficient		0.636	0.901	0.591	0.472	0.629	0.175	0.938
Heart rate error analysis	Mean difference (bpm)	0.4	0.1	0.4	0.4	0.6	0.4	0.4
	Lower limit of confidence difference(bpm)	0.27	-0.38	0.26	-0.11	0.41	0.13	0.33
	Upper limit of confidence difference(bpm)	0.55	0.44	0.5	0.84	0.72	0.68	0.49

Figure 4C1: Evaluation of the equivalence of two devices. Investigational device and ultrasonic Doppler heartbeat signals (control device 2), without averaging process in Group 1

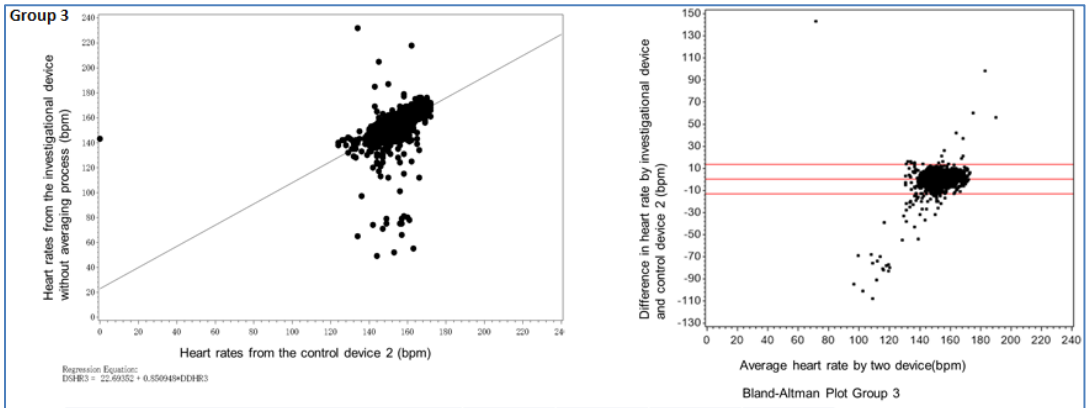
Although overall higher correlation was observed but the group comparison indicated that the correlation tended to be weaker in younger cases.

Heart rate error analysis (Bland-Altman Plot) showed the means differences 0.4 (n=10808) for Group 1 as a whole and individually 0.4 for No.2, 0.0 for No.3, 0.4 for No.4, 0.4 for No.5, 0.6 for No.6, and 0.4 for No.7. Similarly, the same for Group 2 were 0.5 (n=3642) as a whole and individually 0.3 for No.3, 0.8 for No.6. Finally, the same of Group 3 were 0.3 (n=5536) as a whole and 0.6 for No.7, 0.1 for No.9, -0.1 for No.10.



Group 2 (without averaging process)		No.3	No.6	total
Data number of investigational device		2132	1510	3642
Data number of control device 2		2132	1510	3642
Correlation coefficient		0.701	0.783	0.746
Heart rate error analysis	Mean difference (bpm)	0.3	0.8	0.5
	Lower limit of confidence difference(bpm)	0	0.58	0.32
	Upper limit of confidence difference(bpm)	0.58	1.11	0.72

Figure 4C2: Evaluation of the equivalence of two devices. Investigational device and ultrasonic Doppler heartbeat signals (control device 2), without averaging process in Group 2



Group 3 (without averaging process)		No.7	No.9	No.10	total
Data number of investigational device		2510	511	2515	5536
Data number of control device 2		2510	511	2515	5536
Correlation coefficient		0.256	0.309	0.441	0.715
Heart rate error analysis	Mean difference (bpm)	0.6	0.1	-0.1	0.3
	Lower limite of confidence difference(bpm)	0.45	-0.76	-0.35	0.09
	Upper limite of confidence difference(bpm)	0.81	1.03	0.22	0.44

Figure 4C3: Evaluation of the equivalence of two devices. Investigational device and ultrasonic Doppler heartbeat signals (control device 2), without averaging process in Group 3

4. Discussion

In summary, fetal heart rates estimated from abdominal-lead fetal electrocardiograms were in good agreement and high correlation with the same from control device 1 demonstrating its capability to serve a reliable beat by beat

fetal heart rate monitor. On the other hand, 3.75-second mean fetal heart rates computed from electrocardiographic signals of the investigational device were also in good agreement with the same with the control device 2.

The study results demonstrated that the abdominal-lead fetal electrocardiograph could be used for fetal heart rate measurements (beat by beat or averaged) from 24 weeks till 41 weeks of gestation in clinical settings. The study outcomes also suggest that abdominal fetal ECG measurements could be safely carried out even during pregnancy and delivery. In addition, no adverse events directly related to the abdominal-lead fetal electrocardiograph (investigational device) occurred in this trial that confirms the safety of the device. Beat by beat validation with scalp based fetal ECG signals proves that the signals of the investigational machine are actually derived from fetal heart.

Although there were some failures reported in this study, but they were attributed to electrode defects and connection problems only, without having any problem or fault in the investigational device unit itself. However, there are scopes for further improvement in those aspects in the near future.

High correlation coefficient of beat by beat fetal heart rates between the investigational device (abdominal-lead method) and the control device 1 (direct-lead method) could demonstrate a high precision of the investigational device in estimating beat by beat fetal heart rates. The validation of abdominal lead fetal ECG (investigational device) could overcome the inherent limitations of Direct-lead fetal ECG to be able to use only after rupturing uterine membrane requiring electrodes to put on fetal head.

The control device 2 (ultrasound Doppler method) was used to acquire fetal heart rate over 3.75 second window capturing 16 sample points per minute. Averaging on every 3.75 seconds window was previously reported by Dawes et al. in 1991 on the basis of short term variability [9]. Although the limitation of ultrasound Doppler device not being able to estimate the beat by beat fetal heart rates, the high correlation coefficients observed in the comparison of fetal heart rates with the investigational fetal ECG device (after the averaging process on instantaneous heart rates) in this study confirmed that the precision at the level of the doppler based cardiotocomonitor. On the contrary the cardiotocomonitor was found incapable of measuring the precision of 3.75 seconds or higher. In particular, reduced correlation in groups 2 and 3 without averaging process suggest that heart rate variability components at 3.75-second precision contain the major portion of heart rate variability from 24 weeks to 31 weeks of gestation than in group 1. This period is particularly important in clinical fetal monitoring where premature delivery-associated brain disorders such as PVL occur more frequently [10]. In previous animal experiments, relationships of the short-term variability mid and later stages of pregnancy with well-being evaluation and the onset of cerebral palsy were verified [11]. Ultrasound Doppler fetal heartbeat monitoring, which is currently used clinically, only evaluates the fetal heart rate and the health status of the fetus at that time, but cannot test subsequent neurological prognosis, recovery process from the disorder, etc., of fetuses because of its missing information of short term variability of beat by beat fetal heart rate changes. Abdominal-lead fetal ECG device could lead to improvement of the newborn convalescence by evaluating the fetal status timely and correctly with a judgement of timing of termination when it is appropriate by looking at short term variability. In the future, scientific validation of parameters extracted from fetal electrocardiograms in clinical applications of fetal cardiac screening, such as arrhythmia diagnosis [12], cardiac function evaluation [13], diagnosis of cardiac anomalies [14], and well-being evaluation with fine variation [15], are possible.

In conclusion, the study results proved that the fetal ECG obtained from the investigational device was derived from fetal heart. Measurement of non-invasive fetal ECG has been successfully obtained on and after 24 weeks and fetal heart rate measurements were in good agreement with the same obtained by conventional devices (direct lead scalp fetal ECG and Doppler Cardiogram). This study also confirmed that long term abdominal-lead fetal ECG could be carried out in a bedside setting without needing a special examination room, such as a shielded room and to be

safely usable for measurements without affecting the mother or fetus. However, more clinical researches are needed to evaluate short term variability in normal fetuses, and diagnosis of fetal distress or abnormality by using the non-invasive abdominal lead fetal ECG technology.

5. Acknowledgments

This trial was performed as a clinical trial of ATOM Medical Co. supported by Translational Research Network Program of Japan Agency for Medical Research and Development (AMED).

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