Are static fetal growth charts still suitable for diagnostic purposes?

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Abstract

Fetal growth curves and the corresponding interpretation of biometric data represent an essential diagnostic tool in clinical practice and for epidemiological studies, but their validity is questioned by the population-reshuffling phenomenon and by other factors. To restore their diagnostic effectiveness, a suitable interpretative model has to be developed based on new parameters and on a global approach for data collection. To achieve this goal we studied the combined adoption of multidimensional analysis and of cloud-based data-harvesting techniques to produce customized curves more suitable for diagnostic purposes. In particular, multidimensional analysis allows to identify and to avoid more effectively false positives and/or false negatives while the use of cloud allows collecting and processing data on a global scale. The feasibility of the proposed approach is discussed referring to a prototype and a test on the field on a small scale.

1. Introduction

Currently, we are witnessing of an ever more rapid growth in the amount of data and medical information (*data-intensive healthcare*) for which healthcare organizations do not have suitable analysis tools and methods.

A key challenge in such a scenario consists in defining new approaches to data collection in the medical field in order to analyze, visualize and share information that could be useful in decision-making processes and hence to take advantage from the big amount of accumulating clinical data in order to extract useful knowledge and understand patterns and trends within the data. In particular, during the whole perinatal period, routine assessment of fetal growth can be useful only when the medical data are viewed as a continuum over time; this because single biometric parameters measures are only partially useful by themselves, but the trend in such measures, observed over weeks or months for example, may provide the first suspicion to potential medical problems.

Monitoring of intrauterine growth and early detection of fetal growth restriction constitute one of the most challenging goals for obstetricians today as an indispensable step for improving perinatal outcome.

As shown in *Figure 1*, the typical growth curve has three main lines: the middle one represents the 50th percentile or median, the other two are the boundary values. Biometric measurements are often plotted and compared with these kind of reference curves, and are considered to be normal, too low (when below the 5th percentile) or too high (when above the 95th percentile) [1]. They can thus be used as a screening test to recognize those fetuses with borderline biometric measurements that may be associated with, for example, growth restriction, structural or chromosomal abnormalities or macrosomia. However, it has been recognized that customized methods, which take account of the fetus individual growth or individual environment, may better serve the purpose to judge whether a fetus growth progresses normally or not.

Figure 1. A typical fetal growth curve related to the Biparietal Diameter parameter

The reference growth curves currently used in the most of perinatal centers are negatively influenced by several factors, which negatively affect their diagnostic usefulness:

- the data obsolescence which results in a uselessness due to the well known biometric variations of populations over the years;

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- the population reshuffling phenomenon due to the ever-increasing mobility of people;
- the heterogeneity of methods used to define the different reference curves;
- the lack of a global approach to integrate all informative resources coming from the different countries;
- the fact that no single study has sufficient samples to produce charts potentially applicable to all newborns (about 160 millions per year in the world, in 2012).

The data obsolescence is the major limitation, considering that most of the reference charts known in literature and used in clinical practice are up to five decades old [2][3][4] and therefore they are not anymore suitable to reflect the lifestyles characterizing our society.

The paper is organized as follows: in section two we motivate the problem and contextualize the literature background. In Section three we discuss our proposal by defining the main technical aspects and the system architecture. Section four is for results and discussions. The last Section is for conclusions and future works.

2. Motivation and background

Several approaches to improve the ability of fetal biometry to detect potential high-risk fetuses have been proposed and developed in literature:

- the measured biometric parameters can be compared with a customized reference curve [5];
- parameters can be integrated into a formula (e.g. for estimation of fetal weight) [6][7];
- parameters can be assessed each other (proportionality index) [8][9][10];
- parameters can be measured and assessed longitudinally (speed or rate of growth) [11][12].

However, the use of cross-sectional growth curves remains the most widely used method of screening for fetal growth abnormalities.

Gardosi firstly introduced the idea of individualized fetal growth charts according to specific maternal and fetal characteristics in 1992 [5]. The proposal was based on proprietary software and on a centralized approach. Unfortunately, after about 20 years from the interesting proposal, in our knowledge we have no evidence, in the scientific literature, of significant advancement in the availability of global and dynamic reference growth charts.

Later, other authors, starting from a more classic approach, provided different studies by considering homogeneous subgroups of population [13] and by refining the statistical and mathematical approach used to produce the reference curves by using centiles [17]. Nevertheless, the consequent and considerable methodological heterogeneity has made these studies difficult to use for diagnostic purposes. As a consequence, in clinical practice, generic charts are preferred to specific ones, or to more complex approaches based on suitable mathematic models, because of their feasibility. The ethnicity is not the only feature to take into account. There are numerous causes for sub-optimal fetal growth and development. They include: genetic factors; maternal characteristics such as nutrition, education, pregnancy at a very early age, unhealthy lifestyle; complications of pregnancy; physical and socio-economic position at birth, and factors in the environment; disease states, malaria/HIV; intergenerational effects; physical work during pregnancy; tobacco and alcohol use. Addressing the above factors requires a comprehensive approach. A concrete strategy that brings together all these issues, however, does not exist.

Population-specific fetal growth curves are not the solution to the problem since fetal biometric parameters can show high degree of variation in evaluated population from country to country and from area to area, within the same country. Moreover, the majority of reference curves are not available in a reachable, accessible and unique place, so that doctors and patients cannot access to these data in order to make the proper and desired analysis. As a consequence, the adoption of wrong reference charts on specific fetuses could bring to identify suspected small for gestational age (SGA) or large for gestational age (LGA). This means that often is difficult to differentiate between fetuses that are small because of pathologic reasons and fetuses that are small for constitution (they have reached their individual growth potential). All these considerations confirm and validate the need of a new and global approach able to develop dynamic and customized growth curves since they could provide an accurate assessment for the different anthropometrical fetal variables with respect to the static ones.

In this paper we propose an online system exploiting multidimensional analysis for creating customized fetal growth curves, which are sized for a global approach and which allow to perform dynamic analysis in order to make them patient-specific and to considerably reduce the rate of false-positive diagnosis of SGA/LGA which increase the risks of intrapartum and neonatal complications. In our knowledge, the only study which took account more than one variable in fetal diagnosis is that of Naito et al. in 2010 [18] who proposed a multidimensional view of the standard for the development process of human fetuses, by adopting a logistic function with three parameters and a nonlinear regression method. The "multi-

dimensionality" is, hence, viewed by a statistic point of view, and it proved that some individuals within the normal range in a one-dimensional analysis were out of the normal range in the multidimensional one. The whole knowledge of the observed phenomenon, and hence the knowledge of all the factors affecting fetal growth and therefore conditioned both by mother and by fetus, is the key challenge in the study of knowledge extraction from Big Data. It can happen to not have the availability of some data, which are important for the analysis. For instance, may be unknown the fact that a mother smokes or not, or the fact that a mother suffers for an allergy. The question is "how to deal with this incompleteness at the level of analysis?" Although incomplete information is very common to real data, this area has received less attention in the research community than other areas [19], in fact, while multidimensional data models that store and manage complete information have been studied extensively, there are only a few papers that address incomplete information for multidimensional databases. Dyreson [20] first wrote about incomplete information in a multidimensional database context, developing data cube containing regions of unknown values; Barbará and Sullivan [21] wrote about quasi-cubes, in which regions of an eager were replaced with a single approximated value. Which strategy to use is strictly dependent on the kind of incomplete information and also on where it occurs in the multidimensional database.

3. The proposal

In this section we present the technical solution, the mathematical model, which is on the basis of the proposed approach and we briefly describe the architecture of the proposed system, introducing also the user interface.

3.1. Technical solution

The possibility to construct dynamic and customized fetal growth curves is mainly based on the application of multidimensional analysis techniques, which allow us to identify groups of patients (in our case fetuses) who share similar growth patterns over time. The ultrasound exam is modeled by means of Dimensional Fact Model (DFM) [22], where each relevant and influential variable is modeled as a dimension of analysis (we have identified 9 main dimensions), while each biometric parameter analyzed during the exam, is considered as a measure (Figure **2**).

This schema can be thought as it were a database able to answer to queries expressed in the form: "*select the normal range associated to the X biometric parameter of a Y-weeks old fetus belonging to the subgroup defined by the Z dimensional parameters*".

In order to answer to such a kind of queries, an appropriate star schema, which represents multidimensional data, has to be designed and implemented. Such a schema outcomes after the application of ETL (Extraction, Transformation and Loading) flows, which are responsible for collecting data from different data sources, transformation, and cleansing to comply with the target model. To cope with incomplete information issue stated in previous section, several strategies for managing this kind of information could be adopted [23]. Since the term "incomplete" covers several meanings, such as fuzzy, imprecise, indeterminate, indefinite, missing, partial, possible, probabilistic, unknown, uncertain, and vague information, an open issue is represented to the need to classify and correlate all these kind of different meanings according to the necessity. The incompleteness may occur at different levels: at the level of the database (the doctor or the patient has not entered all the required data), at the level of derived data (i.e. the values in the hierarchy), at the level of dimension (one of the dimensions of the cube is not correctly specified, e.g. the smoking habit or disease). According to the type of incompleteness, different strategies can be adopted. From the technical point of view, apart from the incompleteness, and hence the *"sparsity"* characterizing the multidimensional cube, the scalability represents another open issue. In [24] we have proved that the problem largely exceeds the computation capabilities of a classic multidimensional analysis system. Moreover, given the inner distributed nature of the phenomenon, the granularity of data sources cannot be greater than that of the countries involved in the experiment. A partitioning is needed since each country is regulated by specific laws on health data management (privacy, security, accountability etc.).

3.2. System Architecture

The block architecture of the proposed system is illustrated in Figure **3** and it shows three main portions, which correspond to the particular implemented features: acquisition, design and storage and access. In Figure **4** are represented the possible data sources since an interesting feature of our proposal stands exactly in the data harvesting, which can be implemented in three main manners:

1. Data can be inserted by means of direct input (manual) performed by doctors and/or patients. This is the widely adopted method by clinicians who typically handle such information on paper, and hence they transcribe hand-written worksheets.

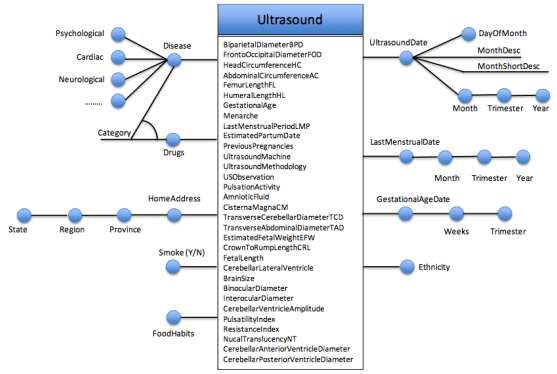

Figure 2. Dimensional Fact Model related to the Ultrasound Visit

2. Data can be collected directly at the source, i.e. at the output of the medical equipment used for the assessment of fetal biometric parameters, such as the traditional Ultrasound machine. In this case, the adopted standard for the distribution and viewing of medical images is the DICOM (Digital Imaging and Communications in Medicine) standard, which allows obtaining discrete values directly from its headers.
3. Data can be inserted by uploading ultrasound pictures coming from the clinical practice (doctors' printed archives) or from the exams (patients' printed report). In this case the images are acquired, scanned and converted in the TIFF format.

The last two methods allow a direct and automatic data transfer and would improve workflow, eliminate potential sources of error and reduce the "*sparsity*" that has been cited in the previous subsection.

The latter method can be made possible by the Optical Character Recognition (OCR) subsystem, which is in charge to analyze and extract textual data directly from ultrasound pictures which are typically accompanied by measurements (biometric parameters with the corresponding values), calculations (gestational age measured in weeks), and descriptive data (ultrasound machine information, exam date, patient's data, and so on). The OCR methodology will be described in subsection 3.4.

These kind of data sources will contribute to feed the curves collection and hence to enrich the DoDs, which will be interrogated, via appropriate interfaces, by the two modules:

- Fetal Growth Curves Builder & Comparison (FGC B&C), which is responsible for the development of customized fetal growth curves and for the comparison among the different available growth curves.
- Multidimensional Builder (MUDIB), which allows performing the dynamic navigation (multidimensional analysis) through the available data, hence representing the fetal growth charts according to different analysis parameters. Users can navigate among high and low precision views of the same aggregate data using drill-down and roll-up operations, which increase and decrease the precision respectively.

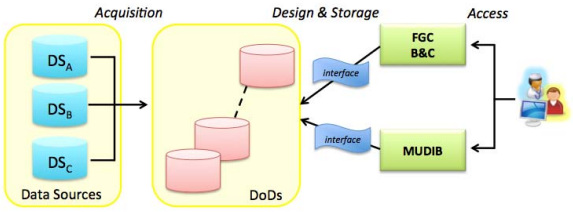

Figure 3. Block architecture of the proposed system

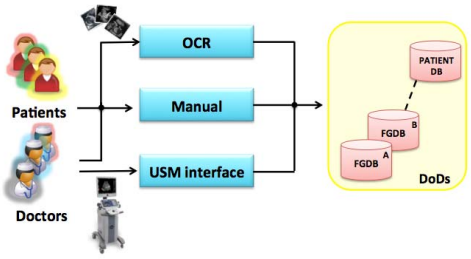

Figure 4. Input data sources

The development of the fetal growth curves is mainly based on the construction of "reference intervals" which are determined starting from the specific samples provided by doctor (direct inputs or ultrasound pictures). On the other hand, the comparison among curves can be performed by doctors who want to visually determine how their own curves differ among others or by families who want to visually understand how much the biometric measure of their fetus deviate from the reference pattern.

3.3. Mathematical Model

From the mathematical and statistical point of view, the construction of such reference intervals for fetal growth curves has been deeply investigated and refined.

Starting from the efforts made by authors such as Royston [25] and Altman and Chitty [26], the choice of a suitable and standard methodology has become obvious and crucial, because inaccurate centiles obtained from an inferior method may mislead the obstetrician as to the true state of health or development of the fetus and increase the chance of suboptimal clinical care.

In literature, several authors provided different studies (most of which adopts a cross-sectional approach) by considering subgroups of population and by defining the statistical and mathematical approach used to produce the reference charts. All methods are based upon regression modeling of both the mean and the standard deviation across gestational age, choosing the polynomial curve, which better fits the model of the samples.

Other authors [27] developed methods based on Z-scores to select a fetal biometric reference curve, analyzing the effect of choice on the quality of screening for growth abnormalities.

In our work we refine the classical mathematical equations commonly used adopting regression analysis approach, which allows constructing the reference curves of the analyzed population according to the different gestational ages. In particular, to obtain the interpolating curve to the experimental data, we have adopted the Least Mean Squares (LMS) technique, which is based on the minimization of the sum of squares of the deviations of each measure by the approximating curve, using a polynomial of any order in order to make the "best fit". Being the curves modeled by polynomials, we talk about multiple linear regression, whose model is in the form showed in (1).

$$Y_i = \beta_0 + \beta_1 X_i + \beta_2 {X_i}^2 + \ldots + \beta_r {X_i}^r \quad (1)$$

where β_0 is the known term, while $\beta_1, \beta_2, .., \beta_r$ are the regression coefficients.

Since is almost never plausible to hypothesize a deterministic relation, we have to consider the presence of an error variable which is a random variable that summarizes our ignorance about the true relationship between X and Y.

$$Y_i = \beta_0 + \beta_1 X_i + \beta_2 {X_i}^2 + \ldots + \beta_r {X_i}^r + \varepsilon_i \quad (2)$$

The objective is to find the vector of least squares estimators of the parameter β (representing the coefficients of the polynomial) that minimizes a cost function L (3) thought of as the sum of the squared deviations of the observations from the true regression model (average gap between what the model predicts and what we measure).

$$L = \sum_{i=1}^{n} {\varepsilon_i}^2 = \sum_{i=1}^{n} (y_i - \beta_0 - \sum_{j=1}^{k} \beta_j x_{ij})^2$$

$$= \varepsilon^T \varepsilon = (y - X\beta)^T (y - X\beta) \quad (3)$$

And so,

$$\hat{\beta} = (X^T X)^{-1} X^T y \quad (4)$$

Writing the model in a more compact way:

$$y = X\beta + \varepsilon \quad (5)$$

$$\hat{\beta} = \arg\min_{\beta} \|y - X\beta\|^2 \quad (6)$$

Least squares techniques are popular for solving inverse problems because they lead to the easiest computations, but they suffer from a main drawback: the lack of robustness to potential outliers, i.e. their strong sensitivity to a small number of large errors in the data set, and in the case of collection of biometric data, the outliers are mostly present.

An important and essential assumption for the mathematical modeling of the phenomenon is about the samples' distribution, that is a Gaussian distribution with a mean and a standard deviation by which is possible to identify that a certain number of samples satisfy some average value of a certain biometric parameter. This assumption allows defining the centile curve by using the well-known formula:

$$Centile = mean + K * SD$$

where K is the corresponding centile of the standard Gaussian distribution. In Figure **5** is demonstrated how, by fixing certain values of gestational age, the corresponding value representing the biometric parameter measure denotes the mean on which the Gaussian is centered (situated on the regression curve).

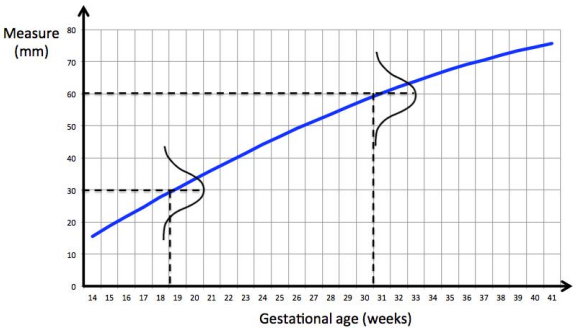

Figure 5. Fetal growth curve seen as a set of Gaussians

3.4. User Interface and Presentation Aspects

As stated before, an interesting feature of our proposal stands in the data harvesting. In order to show how a general doctor can adopt the proposed system in his/her daily work practice, we introduce the Graphic User Interface we have realized related to the key functionalities according to doctors and families.

The doctor who accesses to the system for the first time and wants to upload his/her first ultrasound

image, he/she has to set the ultrasound machine before the OCR in order to correctly divide the areas of the picture and the potential fields that could be present in them. This is performed by a simple step-by-step procedure. The first stage is illustrated in Figure **6**.

Once selected the ultrasound picture, which will work as a template image for that specific doctor, the user has to insert the required ultrasound machine information (brand, model and eventual annotation) in order to associate to that particular doctor his/her specific ultrasound machine.

Families often prefer simplicity and immediateness with respect to mathematical specificity and correctness. So, the patient's interface simply shows a graph containing the reference national growth curves (related to the previous-inserted mother's nationality) and the punctual values of the measured parameters in order to check if the measured values fall within the reference ranges (Figure **7**).

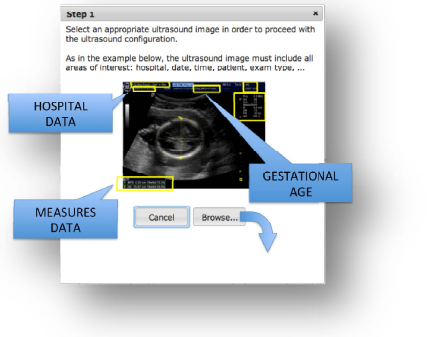

Figure 6. First step for the upload process needed for the Ultrasound Machine registration

Figure 7. Patient interface for the baby's story

4. Results and discussions

In order to validate the system and to show first results, we have performed a test on the field in collaboration with the Public Health Authority (ASL) of Lecce (South East of Italy) with a small sample.

The obstetric group gave us about 500 ultrasound pictures related to Italian women undergoing ultrasound examination between the 11th and 41th weeks of gestation at Vito Fazzi Hospital - Lecce, between November 2012 and September 2013. Measurements of Biparietal Diameter (BPD), Head Circumference (HC), Abdominal Circumference (AC) and Femur Length (FL) were obtained by means of the standard obstetric ultrasound equipment.

The acquired pictures have been then processed through our OCR subsystem, which has been able to correctly recognize almost all the included text with no crucial errors. The OCR is based on the Microsoft Document Imaging Library. For our purposes the OCR has been calibrated for ultrasound pictures by using a training set composed by 300 pictures (150 coming from a General Electric Ultrasound Machine and 150 from a Philips Ultrasound Machine) in order to achieve an overall accuracy greater than 99.50%.

We have then compared the generated curves with those developed by Giorlandino et al. [17] as reference growth curves for the Italian population and those developed by Johnsen et al. [29] as reference growth curves for the European population, in order to quantify and analyze the impact of the adoption of wrong growth reference charts on fetal diagnoses.

Results show that AC and HC biometric parameters follow more or less the same Italian and European trend according to the gestational age. In fact, no significant differences were observed in the values measured during the different growth stages. The BPD and FL parameters, instead, present a little variability. As shown in Figure **8** the Salentinian FL values are always greater then 7 mm.

Clearly, this variability has to be medically investigated since it can be due to several reasons: equipment or measurement errors, genetic variability of the analyzed population, wrong statistic methodologies, selection criteria and so on. In any case, the measured variability is useful to demonstrate the effectiveness of the proposed approach.

The complete set of curves and the complete description of the mathematical procedure adopted for the analysis are published and described at http://www.fpgt.unisalento.it/FPGT/Projects/scientificFoundations.php.

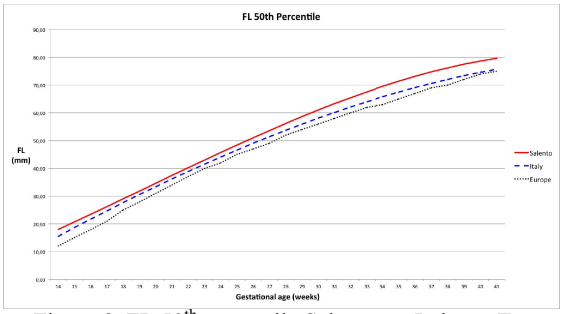

Figure 8. FL 50th percentile Salento vs. Italy vs. Europe

In order to quantify the impact of the adoption of wrong growth charts on fetal diagnoses, we have analyzed the samples' trend for each biometric parameter and have then compared it with the Italian and European standard. Results show significant differences between Salentinian FL growth plots and those reported by Giorlandino et al. [17] for Italy and Johnsen et al. [29] for Europe. Our findings require hence that we should carefully re-examine the appropriateness of continued use of currently adopted reference growth curves. In fact, considering for example the Femur Length parameter (which is resulted to be the most variable), Salentinian fetuses present bigger values with respect to those of Italian, as illustrated in Figure **9**. Our findings show that 26% of Salentinian samples are upper the 95th centile.

Considering the European reference centile curves depicted in Figure **10**, which represent respectively the 5th, 10th, 25th, 50th, 75th, 90th and 95th, the Salentinian samples are always above the upper limit especially in the last weeks of gestation. Here the percentage of samples exceeding the limit is even 46%.

Samples above the 95th centile exceed the upper limit and are traditionally used to define LGA. The usage of Italian reference curves on a Salentinian fetus could hence lead to misdiagnosis, which namely could bring to suspect that the fetal growth does not proceed normally.

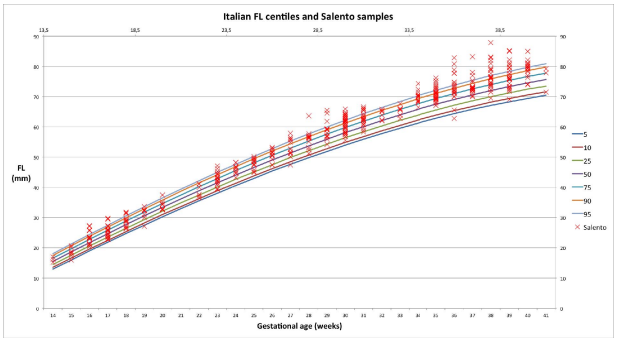

Figure 9. Italian FL centiles and Salentinian samples

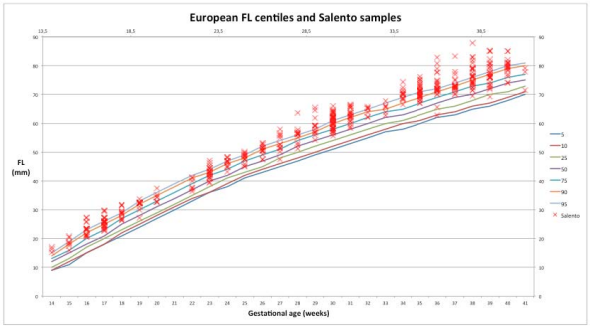

Figure 10. European FL centiles and Salentinian samples

In order to numerically quantify the impact of the adoption of wrong growth charts on fetal diagnoses, we present a quantitative analysis (Figure **11**) which mainly shows the sample number and the percentage value for the FL biometric parameters which exceed the upper limit (95th centile) and the lower one (5th centile) considering the Italian and European reference curves.

	Femur Length					
	Salento		Italy		Europe	
	Samples	***%***	***Samples***	***%***	***Samples***	***%***
> 95th centile	42/437	9,61%	115/437	26,00%	202/437	46%
< 5th centile	30/437	6,86%	1/437	0,20%	0/437	0%

Figure 11. Synthetic and quantitative analysis for FL biometric parameter

In this context, we feel that is strictly necessary to have customized curves for fetal growth in order to provide an accurate fetal assessment and to make the presence of false positive and false negative potentially avoidable.

5. Conclusions

The choice of unsuitable reference curve has a considerable effect on the interpretation of biometric data and consequently on diagnosis process.

Fetal growth curves are extensively adopted to track fetal sizes from the early phases of pregnancy up to delivery. In literature, a large variety of reference charts are reported but they are mostly up to five decades old. Furthermore, they don't address several variables and factors (e.g. ethnicity, foods, lifestyle, smoke, physiological and pathological variables), which are very important for a correct evaluation of the fetal well-being. Therefore, currently adopted fetal growth charts are inadequate to support the melting pot of ethnic groups and lifestyles of our society and continue to use these curves is not appropriate on fetal diagnoses. To solve the problem we propose an online system, which exploits a multidimensional analysis approach to match at run time each new patient with the best cluster of patients having the same characteristics (lifestyle, ethnic group etc.) considering continuously updated measures. The system has been tested on the field for about 6 months and the first results are very promising in terms of increased diagnostic quality. Departments of Obstetrics and Gynecology with which we collaborate assessed the investigation and positively evaluate the functional correctness of the proposed model and approach, the simplicity and usability of the entire system and the correctness and the completeness of the informative model.

In the future the system will be tested on a wider geographic area and with a more extended set of patients, including pediatric ones. An additional and possible direction can be also that of comparing our results with those reached by Naito et al. with the

multidimensional analysis from the statistical point of view.

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