Accuracy of Change in Maternal Serum Alfa Fetoprotein as a Diagnostic Test for Quantitative Assessment of Feto-Maternal Hemorrhage

Thesis

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Abbr.	Full-term
AUROC	: Area under Receiver-operating characteristic curve
CTG	: Cardiotocography
CVS	: Chorionic villious sampling
DAT	: direct antiglobin test
EDTA	: Ethylenediaminetetraacetic acid
EST	: Endodermal sinus tumour
FHR	: Fetal heart rate
FMH	: Fetomaternal haemorrhage
IUD	: Intrauterine death
IVT	: Intravascular intrauterine transfusion
KBT	: Kleiheauer-Betke test
MCA	: Middle cerebral artery
MoM	: Multiples of median
MSAFP	: Maternal serum alfa-feto protein
NPV	: Negative predictive value
PBS	: Phosphate buffered saline
PPV	: Positive predictive value
PSV	: Peak systolic velocity
PV	: Per-vaginal
RAAP	: Routine antenatal anti-D prophylaxis
RBCs	: Red blood cells
RhD	: Rhesus D
ROCcurve	: Receiver-operating characteristic curve

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Introduction

Feto-maternal hemorrhage is considered to be a grave complication which may occur during pregnancy. And due to its graveness the feto-maternal hemorrhage renders the pregnancy as a high risk condition so it must be diagnosed, followed and managed properly in order to avoid any hazards on the mother and the fetus ***(Sebring et al., 1990)***.

Fetal and maternal circulations normally are supposed not to be in direct contact. The placental barrier is found there to play the role of separation between them in a way that receiving nutrients by the fetus and gas exchange between mother and fetus, are not compromised whatsoever. That is why the placental abnormalities are the most encountered risk factor in cases that are confirmed to be suffering from feto-maternal hemorrhage ***(Bernstein et al., 1992).***

In normal pregnancy this abnormal contact between the fetal and maternal circulations may occur so late during delivery. Up to 1 ml of blood may pass. But in an abnormal pregnancy, feto-maternal hemorrhage is defined as the hemorrhage of 30 ml or more, of whole blood from a fetus into the maternal circulation. As less than 30 ml is considered benign and passeswithout any remarkable side effects ***(Sebringet al., 1990).***

Theprobleminfeto-maternalhemorrhageappearswhenfetalblood escapesintothematernalcirculationinaconsiderableamount30 mlormore.Thatshallcompromisethefetalconditionleadingto manymorbiditiesandmortalities.Theresultvariesfromminimal degreeoffetalanemiauptoseveredegreeoffetalanemia ***(Zizka et al.,2001)***.

And lethalhydropsfetalis may follow that, leading to fetal cerebral edema, kernicterus, fluid collection in all body spaces, severe pallor and failed circulation (due to the escaping red cells) and eventually ending in death of the fetus***(Zizkaet al.,2001).***

Occurrence of feto-maternal hemorrhage is not a predictable event. Even some actual cases are listed to be of unknown cause ***(Bird et al., 1999).***

Also as a clinical wise, most of the feto-maternal hemorrhage cases never produce these evident signs or symptoms by which a confirmed diagnosis can be made upon, until it is very late ***(Kecskes, 2003).***

But somehow it might be linked to certain risk factors which if happened to the pregnant lady before in her obstetrical medical history, it gives a clue that this lady in particular is more susceptible for having feto-maternal hemorrhage in her next pregnancies.So more antenatal care

and cautious follow up must be given to such lady in order to avoid any complications as possible and also to detect occurrence of the feto-maternal hemorrhage as earliest so that the management she will be having,could give more optimum outcome ***(Sebringet al., 1990).***

These risk factors include a previous history of spontaneous stillbirth, placental disruption and abnormalities ***(Bernstein et al., 1992),*** anterior position of the placenta, surgical and manual removal of the placenta, twin (monochorionic,monozygotic) pregnancy, premature rupture of membranes, invasive diagnostic procedures as cordocentesis, preterm labor, post maturity, maternal trauma, external version, vaginal assisted delivery, cesarean sectionor massive blood loss during pregnancy***(David et al., 2004).***

Quantification of feto-maternal hemorrhage isdone when severe FMH is suspected and accordingly dose can be adjusted. Additional dose of10 IU of anti-D should be given for every additional 0.5 mL of fetal RBCs in maternal circulation ***(White et al., 2009).***

Methods for quantification of FMH:

Kleihauer–Betke test is the gold standard test for quantification of FMH ***(Maciulevicieneet al., 2008).***

The controversy appears in that Kleihaeur -Betke test is a test which requires a specific laboratory setting and a highly performing hematology specialist so it is not that easy to be conducted and to give reliable results ***(Agarwal et al., 2011).***

There are many disadvantages to the Kleihauer-Betke test, firstly it is subjected to the human error (in the microscopic manual method) andthe time between sampling and testing, if prolonged, this may lead to clotting of the sample and consequently false interpretation (in both of the microscopic manual and the microscopic automated methods)***(Lachman et al., 1977).***

There is flow cytometry method which is detecting fetal red cells in the maternal blood by using anti-fetal red cells antibodies ***(Pelikan et al., 2004).***

Another trial worked on detecting the genomic material of the nucleated fetal red cells using molecular biology techniques**.** Both methods showed promising results, but still more work is needed to accredit them as substitutes to the standard Kleihaeur –Betke test***(Hiromiet al.,1995).***

Alpha- fetoprotein (AFP) is found in both fetal serum and also amniotic fluid. This protein is produced early in gestation by the fetal yolk sac and then later in the liver and gastrointestinal tract. The true function of AFP is unknown ***(Johnson et al., 2012).***

It is considered to be one of the most important markers which are used nowadays in early screening and diagnosis of many of high risk conditions and fetal abnormalities and malformations during pregnancy ***(Firouzbadi et al., 2010).***

For example maternal serum level of the Alpha-Fetoprotein is found by evidence to be raised hugely if the fetus has nervous system malformations as neural tube defects (example Spina bifida and anencephaly) or Down syndrome ***(Wang et al., 2009).***

Since fetal serum level of Alpha-Fetoprotein is found by evidence to be raised in cases of severe fetal anemia, so estimation of maternal serum level of Alpha-Fetoprotein may act as a new method for detection of occurrence of feto-maternal hemorrhage in cases of women at risk of fetal anemia ***(Bartha et al., 2006).***

This recommended new method shall overcome disadvantages of the standard Kleihaeur-Betke test and also it has the advantage of its stability. So storage of samples shall never give false results as in Kleihauer-Betke test ***(Lachman et al., 1977).***

Many studies were working on finding the link betweenelevated maternal serum level of Alpha-Fetoprotein

and cases of women who are known to be complaining of previous severalattacks of vaginalbleeding and feto-maternal hemorrhage especially when accompanied with riskfactors as placental abnormalities ***(Bernstein et al., 1992),*** undergoingprocedure of cordocentesis***(Van Selm et al., 2005)*** and preterm delivery***(Williams et al., 1992).***

No available well conducted study in the literature assesrising maternal serum level of alpha fetoprotein in assessment ofintrapartumfeto-maternal hemorrhage.

Aim of the Work

Study question:

In pregnant women undergoing vaginal delivery, is the change in maternal serum Alpha fetoprotein, before and after delivery, accurate in the quantification of FMH?

Study hypothesis:

We hypothesize that, in pregnant women undergoing vaginal delivery, the change in maternal serum Alpha fetoprotein, before and after delivery, is accurate in quantification of FMH.

Aim of the work:

To find an easier and cheaper test for detection and quantification of FMH, with less inter- and intra- observer variation than the standard KBT.