REVIEW ARTICLE

Systems Thinking Approach on Foetal Abnormalities Associated with Alpha-Fetoprotein Level

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ABSTRACT

Foetal complications associated with abnormal Alpha-Fetoprotein (AFP) levels are becoming a serious matter. The risk of adverse pregnancy outcomes (APOs) is substantially greater in the raised maternal serum-alpha fetoprotein (MS-AFP) group than in the normal MS-AFP group. The top three APOs in terms of occurrence rate in the increased MS-AFP group were structural foetal abnormalities, spontaneous abortion, and premature delivery. Low levels of AFP in the maternal may indicate a risk of Down syndrome (DS). This is an important matter that needs to be investigated and dealt with promptly. This research aims to investigate methods of diagnosis and screening on AFP foetal based on system thinking. It applies the systems thinking approach on foetal complications associated with AFP level from a theoretical perspective. The purpose is to provide an analytical and integrated method to deal with foetal complications associated with AFP level. This integrated approach comprises various analytical aspects, including conceptual framework, data analysis, evaluation of the diagnostic and screening methods. How systems thinking can contribute to improving all these aspects of foetal complication will be investigated. A systematic review of literature from various databases was conducted. The methodology also enabled a detailed explanation of the major problems of AFP in the form of a causal loop diagram based on the holistic view of the systems thinking approach. This research is expected to contribute in various ways on how systems thinking can contribute to overcoming foetal abnormalities associated with abnormal AFP levels. It is expected that the application of a systems approach could provide an effective method of analysis for understanding and managing the foetal abnormalities by considering all aspects in a holistic manner and clearer methods of intervention to reduce the cases.

Keywords
Alpha-fetoprotein, maternal screening, foetal abnormalities, systems thinking

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INTRODUCTION

Birth defects lead to about 5-7% of deaths annually in developing countries, and this percentage is gradually rising.[1] This evidently indicates that pregnancy-related problems are becoming a serious matter, especially foetal complications associated with abnormal Alpha-Fetoprotein (AFP) levels. According to the World Health Organization (WHO), there were nearly 300,000 maternal mortalities globally in 2013, and more than one and a half million women experienced pregnancy-related issues throughout pregnancy and childbirth each year. The implications of acute maternal disorders, involving death and disabilities, represent the greatest challenge of women's disease in developing countries.[2] Maternal serum alpha-fetoprotein (AFP) levels about the first and second trimester of pregnancy are modified in pregnancies with aneuploidy, neural tube defects (NTD) and poor birth result, like foetal death, pre-eclampsia (PE), foetal growth restriction and preterm delivery.[3] This study aims to investigate the problem of AFP and its implications based on the systems thinking approach. It investigates the effectiveness of current methods of screening and intervention, its shortcoming and how a systems approach can contribute to solving the problem.

Methodology

The Cochrane Reviewers' Handbook technique was used to facilitate the literature review and research process. The procedure for identifying primary studies based on appropriate analysis and causal factor characteristics was adopted in the study protocol. Articles were critically examined, and basic data based on objectives, design, causal aspects, and outcomes were obtained. Search strategy planning was defined based on the main elements of the problem and natural language terminologies were used for subject description. The search was focused on comparisons, outcomes, results from the analysis, abstracts and full texts displaying the subject, components of comparison and outcomes. The effectiveness of the current diagnosis methods was reviewed to identify the development of the diagnosis technique from the early 2000s until the present. The publication language was limited to English.

The selection criteria of the study for the concept and application included theoretical knowledge and study which relates to foetal complication. The theoretical and analytical data collected was interpreted by systems thinking. For the effectiveness of the current diagnosis, the study's selection criteria focused on the diagnosis of foetal complications associated with AFP level.

Conceptualizing Foetal Abnormalities Associated with Alpha-fetoprotein (AFP)

According to the National Library of Medicine (2020), a protein called alpha-fetoprotein (AFP) is generated in the liver of a growing foetus.[4] Some AFP crosses through the placenta and into the mother's blood during the baby's growth.[4] During the second trimester of pregnancy, an AFP test is used to determine the amount of AFP in pregnant women.[4] A high or low level of AFP in a mother's blood might indicate a birth defect or other problems.[4] According to Pranpanus et al. (2021), AFP levels are likely to increase with advanced pregnancy after about 17 weeks and levels are greater in patients who had a lower body weight.[5] The serum levels of AFP in Down Syndrome (DS) foetuses were less than in normal foetuses.[5]

As increased or decreased levels of AFP in maternal indicate a high chance of foetus abnormalities, thus, further testing is necessary to determine the amount of risk. Although many women with high maternal AFP do not have foetus abnormalities, there is a higher risk of obstetric problems such as premature rupture of membranes, placenta accreta, increta, and percreta.[5] According to the current studies, patients with a lower maternal body weight had higher serum AFP concentrations. AFP concentrations are usually greater as gestational age-progressed beyond the first trimester, but they dropped as maternal weight increases.[5] This supports the finding that maternal serum levels are affected by maternal weight-adjusted for Multiple of the Median (MoM). As a result, maternal weight adjustment for serum calculation also plays role. Furthermore, some recent studies have revealed that race and ethnicity have a significant impact on serum concentrations in both Down syndrome (DS) and normal foetuses throughout gestation.[5] Other studies have observed discrepancies in normative median serum levels in subgroups of the same nation or ethnicity, indicating that maternal serum quadruple markers do not have universally parameters for screening for Down syndrome in all races and ethnicities.[5] However, the variations in AFP concentrations are not strongly influenced by the maternal weight (Wald et al., 1981). According to Miao et al. (2012), women who gave birth to DS children were substantially older than women who gave birth to non-DS children.[6] In comparison to mothers who gave birth to children without DS, women who gave birth to children with DS had considerably lower AFP MoM levels.[6]

The Major Implications of AFP Abnormality

Low or high levels of AFP in the maternal may indicate a risk of Down Syndrome (DS) or neural tube defect (a severe disorder that causes aberrant development of a growing baby's brain and spine), twins or multiple births, and miscalculation of the due date.[7] All these are the risky implications of AFP levels during pregnancy.[4] For instance, in some countries, such as China, there was 16646 to 22195 occurrences of Down syndrome per 16–20 million births in 2003.[8] According to a study by Miao et al. in 2012, in China, Down syndrome was found to be

present in approximately 0.2% of the population.[6] As a matter of fact, the medical, educational and social expenses of treating new instances of DS are expected to be more than RMB10 billion (about $1.58 billion).[8] These expenditures are paid mostly by families, which frequently results in family hardship.[8] Besides DS, neural tube defect can be one of the major implications of abnormal AFP levels.[8]

Screening Methods

A prenatal diagnosis must be made if a pregnant woman has polyhydramnios or anhydramnios, abnormal foetal development or the foetus is suspected of malformation, early-pregnancy contact with a substance that could cause congenital defects, a family history of genetic diseases or a history of giving birth to an infant with a serious congenital defect or becoming a primipara (having a first child) at the age of 35 or beyond.[9] In practice, doctors often recommended amniocentesis to pregnant women over the age of 35 or who had a family history of congenital disorders.[9]

For the current diagnosis of foetal complications, there are several methods for screening tests during the first and second trimesters. For the first trimester, there are maternal blood screen and ultrasound only, while for the second trimester, there are maternal serum screen, foetal echocardiogram and anomaly ultrasound. If the screening test results are abnormal, doctors will typically recommend additional diagnostic testing to see whether the baby has any birth abnormalities or other concerns. These diagnostic tests may be provided to women who are 35 years old or older, have had a previous pregnancy affected by a birth defect, have chronic diseases such as lupus, high blood pressure, diabetes, or epilepsy, or women who use particular medicines. Contrary to international guidelines, prenatal detection in China has typically depended on invasive maternal age-based testing.[8] The second-trimester triple test [alphafetoprotein (α-FP), human chorionic gonadotrophin (hCG) or free b-hCG, and unconjugated oestriol (uE3)] is the most used screening test methods. Only a few centres in large cities are able to offer alternative screening tests such as the first trimester combined test or the cell-free foetal DNA (cffDNA) blood test. The least affordable test for the great majority of the Chinese people is cffDNA (RMB2400), while the triple test is the most cost-effective (RMB240).[8.] The diagnostic tests include high-resolution ultrasound, chorionic villus sampling (CVS) and amniocentesis.[10]

Despite advancements in prenatal screening, DS remains a difficult condition to diagnose, especially in developing countries.[5] With a prevalence of 1.4:1,000 live births, DS is the most prevalent type of trisomy.[5] Even though there is a more reliable cell-free foetal DNA test, the quadruple test is still used for foetal DS screening, particularly for low-resource countries, due to the high cost of cell-free foetal DNA tests.[5] Many investigations in developing countries have validated the screening effectiveness of this test, with a satisfactory detection rate for DS screening.[5] The AFP PLUS Quad Test will, in total, be able to detect 80% of all pregnancies with DS (Newberger, 2000).

In research conducted by Miao et al. (2012), Wallace LifeCycleTM Elipse analysis software (Perkin Elmer) was used to evaluate the risk of carrying a foetus with DS during the first and second trimesters.[6] Women who were at high risk of carrying a DS foetus were referred to genetic counsellors and provided amniocentesis (weeks 19 to 21 of pregnancy) or cordocentesis (weeks 22 to 28 of pregnancy) for cytogenetic analysis to verify or rule out DS.[6] Participants were given informed consent before performing amniocentesis and cordocentesis, which were both optional.[6] Participants at high risk who refused amniocentesis or cordocentesis, as well as those at low risk, were followed up by reviewing medical records and/ or doing a telephone interview to assess the pregnancy's outcome.[6]

According to Du et al. (2017), the clinical value of a second-trimester ultrasound screening of foetal nasal bone development in identifying chromosomal abnormalities is significant.[11] In pre-screened populations, the absence of foetal nasal bone is a highly specific ultrasonographic diagnostic for identifying chromosomal disorders.[11] Moreover, in the first or early second trimester, incremental use of serological screening, ultrasound screening, and non-invasive DNA testing can

determine if the foetal nasal bone is still a useful ultrasound soft marker in detecting chromosomal abnormalities.[11] Pregnant women above the age of 35 or those found to be at high risk by the screening test were advised on invasive prenatal diagnostic procedures.[11] In addition to foetal nasal bone length, recent studies have shown that prenasal thickness and the prenasal thickness-to-nasal bone length ratio may be performed as efficient soft ultrasonography indicators for DS screening.[11]

A study by Li et al. (2016) in the Hospital of Kunming Medical University, China, reported that there are two categorisations of screening tests performed during the first trimester combined screening, which are pregnancies screened with 'low risk' and 'high risk'.[8] For the 'high risk', cytogenetic tests revealed 22 chromosomal abnormalities in foetuses that underwent karyotyping, including foetuses with trisomy 21, trisomy 18, Turner syndrome, and other chromosomal abnormalities.[8] Prior to delivery, ultrasonography revealed severe structural and cardiac abnormalities in trisomy 21 foetuses in a dizygotic twin pregnancy.[8]

Limitations and Shortcomings of the Current Screening & Diagnosis Methods

Even though maternal serum quadruple screening detection rates are between 75% to 85%, however, these studies also found false-positive screening rates ranging from 5% to 14%, which can result in elevated numbers of invasive procedures and elevated laboratory costs for karyotyping, both of which are bothersome for low-resource countries.[5] According to Prapanus et al. (2021), there is a lack of facilities and funding in developing countries, as well as a general inability to afford the more expensive cell-free foetal DNA test.[5]

The ethnic factor is one of the causes of the high false-positive rates. Literature research conclusions have found that integrating the amiss ethnic factor with various serum marker reference ranges results in a larger percentage of false positives.[5] Furthermore, there is insufficient data on the effectiveness and false positive rate of the quadruple test in many cases. There was a limitation on the setting of the study for the concept and application which focuses on Asia to discover the Asian concept and application of systems thinking relating to this topic.

Systems Approach on Foetal Abnormalities Asociated with (AFP)

Systems thinking is a mindset and a set of technical skills for understanding and problem-solving.[12] According to Guo et al. (2020), systems thinking can assess the importance of system elements by studying the existing whole, allowing for the observation of components and their respective interactions and the finding of the rule of change rather than static slices.[12] For the research methodology, one of the important tools in systems thinking is the system archetype.[12] It has a range of forms and a clear structure, and it highlights the common difficulties of a sequence of events.[12] The purpose of the system archetype is to provide alternatives to enlarge systems' dynamic changes and use it in-depth thought in order to comprehend and solve challenges.[12]

Systems Thinking and Healthcare Delivery

Thinking about healthcare delivery based on a systems approach is termed systems thinking. A health system, in this sense, is a set of connected or interdependent parts or agents, including health professionals and patients, bound by a common purpose.[13] Healthcare is a complex system because of the great number of interconnections within and among systems.[13] Components of a complex and dynamic system made up of separate elements and agents, such as the healthcare providers` systems and patients' systems must be comprehended.[13]

The system of providers is a clinic or hospital where physicians, as well as other healthcare providers, offer patient treatment and assistance, and administrative and even other treatment plans. Clinical programmes and centres, hospitals, community health centres groups, and integrative healthcare institutions all fall under the category of a health care system, which is a set of clinical programmes and centres that are part of a broader organisation. The individuals with whom patients engage, such as their family members and friends, community groups, their physicians, the wider healthcare system, and

healthcare administration experts are all part of the patient's system.[13]

Science of health systems, according to the American Medical Association (AMA), provides tools to understand how healthcare is delivered, how health professionals work together to deliver that care and how the health system can improve health.[13] Systems thinking is the glue that connects the domains of health systems science. Systems thinking allows health professionals to apply a comprehensive, holistic and patient-centred approach to health care.[13] Because health care is a complex web of interdependencies, health professionals must be able to see the whole and recognize multidirectional cause and effect relationships within the system.[13] It also provides a conceptual framework that aids healthcare systems with tools necessary for harnessing the rapid advances in basic biomedical science.[14] Integrating systems thinking in AFP is important because systems thinking promotes real methodological issues and stimulates critical thinking in order to deliver better patient-centred healthcare.[14] Accordingly, systems thinking can be related to AFP as an effective tool to analyse and integrate the screening methods for diagnosis and intervention. It is regarded as a useful platform to make a clear definition of the problem based on a holistic view.

Systems thinking as an effective tool for AFP data analysis

In the case of foetal abnormalities, the AFP system must be attentive to a broader picture.[15] This includes the presence of underlying conditions due to the abnormal level of AFP such as preeclampsia, neural tube defect (NTD), Down syndrome and determination of a diagnosis of the patient which is maternal, the aetiology of the condition and other biochemicals data which affects AFP, the recommended treatment of the patient which related to abnormal AFP level, monitoring from the time of diagnosis until future prediction and the effect of the presence of the condition with AFP level on survival.

Foetal abnormalities must be considered as a system within which the AFP components are involved and evolve over time, producing patterns and trends.[13] Basically, the behaviour-over-time graph can be used as a tool to keep tracking the patterns and trends that these changes produce.[13] The system's major elements relating to AFP that alter the progression of the elements over time can be determined.[15] For instance, offering screening tests for neural tube defects and genetic disorders are becoming routine in prenatal management. Over the last several years, there have been some modifications in the suggested technique of prenatal screening and research is underway to enhance detection performance using better combinations of maternal serum analytes. This may change the patterns and trends of the system if the detection rate progresses well. Hence, the occurrence of foetal abnormalities could quickly decrease over time.[15]

On the other hand, the structure of the AFP system which influences its behaviour must be acknowledged by understanding the foetal abnormalities storyline and problem which is due to AFP in terms of its condition, diagnosis, treatment plan, etc. and matches them into the system archetypes. Another method is to create a causal loop diagram by sketching the links between the main variables or elements that are influencing the foetal abnormalities due to AFP (Figure 3.4 causal loop diagram). Besides, the circular nature of various cause-and-effect connections in foetal abnormalities should be recognized by familiarizing with its AFP production, sample collections for screening elements, the prenatal level throughout the gestation, the screening test of the maternal serum AFP, etc. After recognizing the circular nature of the cause-and-effect relationship, significant linkages between and within the AFP systems can be established.[16]

Assumptions about the AFP should be surfaced and tested. It is important to explore and investigate the link between AFP and a variety of clinicopathological factors and staging systems that relate to foetal abnormalities. Therefore, the effectiveness of the treatment plan can be guaranteed not only to certain diseases or conditions but also applicable to other cases. Another point is that the situation should be considered thoroughly before deciding on the foetal abnormalities. Not all foetal abnormalities are associated with the AFP. Gestational sacs during early pregnancy frequently show defective yolk sac formation,

which is also likely to be due to poor foetal development.[16] In addition, due to oedema, the yolk sac expands and becomes less thick in the early stages of embryonic death, right before or after the foetal heart stops beating. Rather than being the major cause of early pregnancy failure, these differences in yolk sac size and appearance are the result of aberrant foetal growth or death.[16] These are factors affecting foetal abnormalities that should be investigated in depth so as to avoid misinterpreting their treatments and solutions.

According to Ehrlichman (2018), to discover potential leverage actions one must first grasp the AFP system structure.[17] The leverage action that appears most likely to generate desirable results may be executed by analysing the structure, interrelations, and reinforcement inside a system.[17] In a clearer context, leverage is determining where actions and structural changes can result in huge, long-term impacts.[18] As mentioned above, the short-term, long-term, and unexpected effects relating to foetal abnormalities AFP activities must be analysed. For instance, the proper screening and diagnosis of the foetal with a neural tube defect can enhance the success of the condition management.

Systems thinking and neural tube defect associated with AFP

Neural tube abnormalities can be one of the major implications of AFP. According to Rose & Mennuti (2009), neural tube defects can be detected with both ultrasonography and Maternal Serum Alpha-Fetoprotein (MSAFP) screening.[19] The lesion can be seen on ultrasound, and higher MSAFP levels will put the patient in a high-risk group, requiring a thorough foetal ultrasound scan and/or amniocentesis to verify the diagnosis.[19] For this reason, screening reduces morbidity and mortality by facilitating early diagnosis allowing families to make informed reproductive decisions and develop appropriate prenatal care and delivery techniques.[19] Low levels of folic acid have been linked to neural tube defects including spina bifida in the maternal blood of many pregnant women. Women should begin taking folic acid three to four months before conception to provide adequate maternal serum folic acid throughout pregnancy. This is because NTDs occur during the first three months of pregnancy, when the majority of women are not even aware that they are pregnant (Zhu, 2013). Taking note of foetal abnormalities associated with AFP accumulations and rates of change is another important point to realize. Accordingly, an unusual rise in plasma AFP level is thought to be a sign of pathological conditions in adults[20] For several decades, serum AFP has been regarded as the 'gold-standard' biomarker for clinical diagnosis.[20]

AFP has been linked to foetal abnormalities and disorders, and aberrant levels of AFP in maternal blood have been utilised in prenatal screening as a marker for spina bifida or DS. According to Chen et al. (2020), AFP has been utilised as a biomarker to aid treatment decision-making and prognosis analysis in recent years.[20] Physiological, chemical, and immunological characteristics of AFP have all been thoroughly investigated, in addition to its therapeutic potential.[20] Nevertheless, the biological properties of AFP have not been investigated in detail.[20] A little change in the level of AFP could give an impact on foetal abnormalities, and it is important to observe its trends.

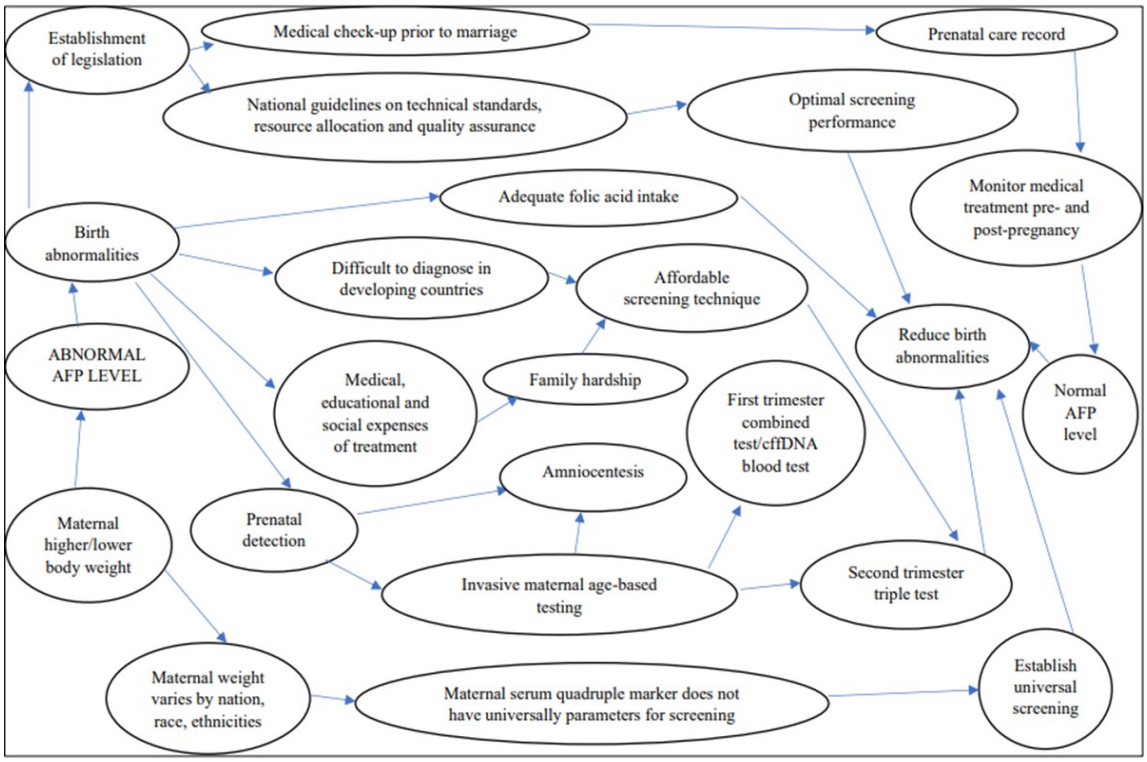
The problem of time delays due to maternal physiological changes

When using AFP as a biomarker to investigate cause-and-effect linkages of foetal anomalies, it is important to be aware of the impact of time delays. The maternal physiological changes make diagnosis difficult and the delay in treatment might have significant implications.[21] Treatment should not be delayed allowing for the discrepancy, i.e., the inconsistency of the medication. Delays caused by diagnostic errors, prolonged diagnosis, or treatment plans increase the risks. According to (Kalumbi et al., 2013), early detection and treatment minimise maternal and foetal morbidity and death considerably.[22] Enhanced obstetrics staff training and the use of detection systems to prevent delays in identification and referral might be beneficial.[23]

As such, results can be evaluated and, if necessary, the entire detection of the foetal abnormalities associated with the AFP system must be changed to achieve "successive

approximation." Assessing the results could be challenging because healthcare practitioners need to decide on the right treatment for the patients. However, if there is any misleading diagnosis, the treatment given might also be incorrect. Before the patient expresses an adverse outcome or results, the healthcare practitioners must thoroughly investigate and diagnose the patient's condition in the right manner. It is not too late to change the diagnosis method earlier rather than quick action in deciding on any treatment. In the final analysis, the system could be achieved successfully due to the detailed and thorough evaluation of each of the components of the system.[21]

The causal loop diagram clearly shows that systems thinking as related to AFP can be an effective tool to analyse and integrate the screening methods for diagnosis and intervention. It shows that DS is the main problem of foetal abnormalities. This condition is associated with the low AFP level of the maternal. Basically, the low maternal body weight can cause a high AFP level which leads to other foetal complications. The different nations, races and ethnicities can be the main source of the different maternal body weight, which can make it hard to find a universal parameter for screening maternal serum quadruple marker. Thus, the causal loop diagram suggests that the way to solve these problems is to establish a universal screening standard. To prevent DS, prenatal detection must be conducted early either by integrated screening or by invasive maternal age-based testing, which includes the first-trimester combined test/cffDNA blood test or second-trimester triple test. For the high risk or positive MSS test, amniocentesis should be conducted. To achieve the best screening results, national rules on technical standards, resource allocation, and quality assurance must be made public and promoted. In addition to national guidelines, ongoing quality control programmes and an evidence base that is continuously updated must be built. Both of these initiatives must be backed by a resource stream (Tu et al., 2016). A nationwide prenatal ultrasound testing guideline recommends that the prenatal ultrasound test be standardised and that practitioners be accredited. To ensure that everyone has equal access to MSS, especially in Asian countries, the entire structure of MSS service delivery should be assessed during policy formulation (Li et al., 2015). A national regulation for the administration of prenatal diagnosis procedures was published by the Chinese Ministry of Health in 2003 with the intention of enabling prospective parents to identify and manage their risk of birth defects, make educated reproductive



Causal loop diagram for foetal abnormalities associated with abnormal AFP level

decisions, and increase the safety of deliveries. Setting a fair price is essential since it affects incentives (Chen et al., 2007). In order to reach a suitable price ratio, the healthcare administration and pricing authority should base the price of health services on unit costs. According to Chen et al. (2007), the government should increase the cost of prenatal diagnostic services while decreasing the cost of serum screening tests to provide a reasonable inducement for the supplier. If the cost of the serum screening test was reduced, prenatal testing for DS would be easier for pregnant women in rural and metropolitan areas.

CONCLUSION

This study aimed at providing an analytical and integrated method, that is based on systems thinking, to approach the problem of foetal complications associated with AFP level. This integrated approach comprised various analytical aspects, including conceptual framework and data analysis, systematic review and assessment of the diagnostic and screening methods. Because health care is a complex web of interdependencies, the systems thinking approach is used to enable health professionals to see the whole problem of foetal complications associated with AFP level and recognize multidirectional cause and effect relationships within the system.

From the section on conceptualizing foetal abnormalities associated with AFP, regulations should be enacted that aim at ensuring the health of maternal and neonatal in order to improve the quality of the new-born population. Since foetal anomalies are difficult to be identified in developing countries, and due to the cost-effect of some screening methods, it is suggested that other screening methods such as first-trimester screening models can be used. Potentiality, the effective method to reduce the rising number of infants born with abnormalities and serious disorders, is maternal-health education and early MSS testing and amniocentesis. Prenatal screening tests can accurately predict a woman's chance of carrying a deformed foetus and assist prevent "imperfect" births, so enhancing the quality of the family's future infant and the country's future population.

In Asian countries, integrated screening was the most successful approach to detecting prenatal anomalies. Integrated screening involves taking measures in both the first and second trimesters and calculating the risk of foetal anomalies. The health ministries of these countries need to play a vital role in reducing foetal abnormalities by developing reproduction technology to track and control family reproduction as well as high-risk pregnancies. With this, medical treatment during the pregnancy, noting prenatal developments, labour and delivery, postpartum follow-up can be monitored. Comprehensive supervision of the women before, during, and after pregnancy, as well as after childbirth should also be taken.

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