Study of Risk Factors and Recurrence of Fetal Congenital Anomalies

Ibrahim Mohiy El-Maghraby[1] (MD) & Gamal Mohamed Hashish[2] (MD)

[1] Fellow, Obstetrics & Gynecology Department, Shibin El Kom Teaching Hospital, Egypt
[2] Assistant Consultant & Head of Obstetrics & Gynecology Department, Shibin El Kom Teaching Hospital, Egypt
Ibrahim_mohie@yahoo.com

Abstract: Background: Congenital abnormalities (CA) represent one of the permanent problem for both of the family and the society. Worldwide, nearly three millions of offsprings yearly born with major congenital abnormalities which represent about 3% of total newborns around the world. Malformation of infants may lead to mortality, more than 70% of foeti can`t survive and die within the first month of life. There are many factors responsible for CA, but about 40-60% of the causes of congenital anomalies not known yet. **Objective:** this study aimed to study of risk factors and recurrence of fetal congenital anomalies. **Patients and methods**: This study was carried out in Kasr El Aini Hospital, High Risk Pregnancy department & Shibin El Kom Teaching Hospital on 1000 pregnant ladies who have fetal congenital anomalies in current pregnancy or those with history of congenital anomalies in previous siblings and 1000 women who have normal pregnancy with no fetal congenital anomalies from October 2016 to August 2017. Full detailed history and examination as well as Full ultrasound scan for assessment of Fetal viability, Position and presentation, Gestational age, Fetal weight, Placental site, Amniotic fluid and Fetal congenital anomalies. **Results:** there was statistically no significant difference (P>0.05) between cases and control groups regarding their age, parity and residence. Also, cases had more frequent medical and drug history, positive family history, as well as positive consanguineous compared to controls with statistically significant difference in between by using chi-square test (P<0.001). Additionally, Drug, radiation exposure and family history were considered the most significant independent predictors of congenital anomalies according to binary logistic regression model results. **Conclusions:** Estimation pregnancy during early stages by using sonography can detect the gestational age, twinning or multiple pregnancies, sex of foetus and early detection of fetal anomalies which in some adverse cases required termination of pregnancy.

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1. Introduction:

Definition of congenital abnormalities (CA) by clinics as defects in structure or function of fetal organs which include metabolic disorders which seen at birth. Many factors mainly of intrinsic origin during prenatal stage play an important role in the occurrence of anomalies. Abnormal division of cells during early embryonic stage (embryogenesis) or failure in development of organs and systems result in such congenital anomalies.

In addition to the congenital abnormalities which occur during prenatal stage, birth defects can also exaggerate the condition and still to be an vital cause of fetal morbidity and mortality **(Francine *et al.*, 2014).**

Based on the World Health Organization (WHO) report, a high number of newly born infants die within first 4weeks of parturition which may reach to 303 000 infants yearly suffering from congenital anomalies worldwide. Congenital abnormalities of infants can contribute to disability for long period, this disability may have important effects on individuals, families, societies and health-care organizations. Heart, neural tube defects and down syndrome considered the most general sever congenital abnormalities among infants. The actual causes of congenital anomalies are unknown in spite of many factors either extrinsic or intrinsic or both may be participating in such condition as: environmental factors, infectious, nutritional and genetic factors. Early detection of congenital defects, some of which can be treated through vaccination, adequate supplementation with folic acid or iodine during gestational period and enough antenatal care etc. **(WHO, 2016).**

In spite of about 50% of all congenital defects cases not known the actual cause,, there are some known factors such as genetic, socioeconomic and demographic factors, environmental factors, maternal infections such as syphilis and rubella and insufficient intake of folic acid during gestation time which increase the possibility for occurring of neural tube defects in the newborn, whereas, intake of vitamin A with large quantities during early stage of gestation may lead to abnormal development of embryo or fetus **(The Global Strategy for Women's, Children's and Adolescents' Health, 2016).**

Cytogenetic examination of chromosomes during gestation for detection of chromosomal abnormalities can be carried out through taking samples from amniocentesis or chronic villi sampling by invasive methods.

For the reason that these methods for obtaining the samples are accompanied with a danger of abortion, the usual approach is to perform non-invasive test to define an individual woman's risk of having a chromosomal abnormal pregnancy **(Bittar, 2008).**

Prenatal examination by using biochemical methods and/or ultrasound examination can be carried out during the late first trimester and /or in the early second trimester **(Al-Jarallah, 2009).**

The pace of development in the fields of imaging, reproductive technology, and genetics promises to accelerate in the years ahead. Medical genetics promises to extend to all stages of the life cycle prenatal, perinatal childhood and adulthood **(Gieffers *et al.*, 2008)**.

Examination of the fetus during prenatal stage for detection of anomalies give the chance for prenatal therapy, and a detailed discussion of pregnancy fate. Moreover, prenatal diagnosis can affect the control and management of condition during antepartum and intrapartum, and allow the scheduling of the method and place of parturition. Simple anatomic anomalies in the foetuses can be treated surgically **(Park *et al.*, 2016).**

Therefore, this study is designed to evaluate ladies who are pregnant in a fetus with one or more congenital anomalies to detect the possibility of recurrence of the same or other anomaly & compare them with a control group to elucidate the possible risk factors for development of congenital anomalies.

2. Patients and Methods

This study was carried out in Kasr El Aini Hospital, High Risk Pregnancy department & Shibin El Kom Teaching Hospital on 1000 pregnant ladies who have fetal congenital anomalies in current pregnancy or those with history of congenital anomalies in previous siblings and 1000 women who have normal pregnancy with no fetal congenital anomalies from October 2016 to August 2017.

Ethical consideration:

All subjects signed a written informed consent with explaining the aim of study, which was developed according to the standard of Quality Improvement System in Ministry of Health in Egypt and modified according ethical committee in Faculty of Medicine, Cairo University.

Inclusion criteria: were age 16-45 years old and singleton viable pregnancy.

Exclusion criteria: multiple pregnancies.

For all neonates, the following procedures were performed:

– **Careful history taking regarding:**

Prenatal history including: maternal age, residence, occupation, socioeconomic state and consanguinity. Husband: name, age, occupation and special habits of medical importance.

Obstetric history: Gravidity & parity, Multiple pregnancies, Maternal disorders during pregnancy e.g. hypertensive disorders and gestational diabetes and History of congenital anomalies in previous pregnancies.

Menstrual history: Last menstrual period.

Family history of: Diabetes mellitus, Hypertension and Congenital anomalies in relatives.

Maternal medical history: Diabetes mellitus, Hypertensive disorders and others.

- **General examination:** Full general examination was done with special concern to: Vital signs: blood pressure, pulse, temperature, heart rat, Chest and heart examination.

- **Abdominal examination:** For assessment of gestational age, fetal lie and presentation, fetal heart sounds, and any scars.

– **Investigations:** Full ultrasound scan for assessment of Fetal viability, Position and presentation, Gestational age, Fetal weight, Placental site, Amniotic fluid and Fetal congenital anomalies.

The ultrasound examination was done on equipment's Medison Accuvix, Medison V20 and GE Volosun which have at least the following: Real time, gray-scale ultrasound capabilities, Trans-abdominal transducers (3–5-MHz range), Adjustable acoustic power output controls with output display standards, Freeze frame capabilities, Electronic callipers, Capacity to print/store images and Regular maintenance and servicing, important for optimal equipment performance.

Ultrasound scan for congenital anomalies included:

– Fetal brain scan for NTDs, ventriculomegaly, holoprosencephaly, DWS, choroid plexus cysts and destructive lesions of the brain.

– Fetal face for cleft lip and palate.

– Fetal neck for cystic hygroma and nuchal fold thickness.

– Fetal chest for pleural effusion, diaphragmatic hernia and cystic lung.

– Fetal heart for septal defects, valve lesions, great arteries anomalies and echogenic foci.

– Fetal abdomen for omphalocele, gastroschisis, intestinal obstructions, abdominal cyst, echogenic bowel and ascites.

– Fetal limes for limb defects, micromyelia, talibus and rocker bottom.

– Fetal hydrops with generalized edema, ascites, pericardial and pleural effusion.

– Data were collected from patients and statistical analysis was done to detect type, recurrence & risk factors of anomalies.

Statistical Analysis:

Results analyzed and tabulated using MICROSOFT EXCEL 2016 and SPSS v. 21. (SPSS Inc., Chicago, IL, USA). Percentage (%), mean and SD. Analytical: includes: Chi-Squared (χ^2), and Fisher exact test. Unpaired t-test was used to compare two groups as regard quantitative variable. A value of $P < 0.05$ was indicated statistically significant.

3. Results:

Table 1: Comparison between cases and controls regarding their age, parity and residence.

Variables	Cases (N=1000)	Controls (N=1000)	X^2	P
Age Mean±SD Range	27.1+5 16-45	26.7+4.5 19-41	1.9 #	$>0.05^{NS}$
Parity Mean±SD Range	2±1 0-6	2±0.6 0-6	t=1.9	$>0.05^{NS}$
Residence Rural Urban	327(32.7%) 673(67.3%)	248(24.8%) 752(75.2%)	$x^2=3$	$>0.05^{NS}$

SD; stander deviation # unpaired t-test x^2: chi-square p: p-value NS: non-significant differences

This table shows no statistically significant difference (P>0.05) between cases and control groups regarding their age, parity and residence.

Table 2: Comparison between cases and controls as regard drug intake during pregnancy

Variables		Cases N=1000		Controls N=1000		X^2	P
		Negative	Positive	Negative	Positive		
Drug Intake During Pregnancy	No.	911	89	939	61	**5.6**	**<0.05** S
	%	91.1%	8.9%	93.9%	6.1%		
Radiation Exposure	No.	994	6	999	1	**4.89**	**<0.05** S
	%	99.4%	0.6%	99.9%	0.1		
Family History of Congenital Anomalies In Relatives	No.	890	110	930	70	**12.37**	**<0.001** HS
	%	89%	11%	93%	7%		

SD; stander deviation x^2: chi-square p: p-value S: significant HS: highly significant differences

This table shows that cases had more frequent drug intake during pregnancy compared to controls with statistically significant difference in between by using chi-square test. While, cases had more frequent exposure to radiation compared to controls with statistically significant difference in between by using Fisher exact test. Also, cases had more frequent positive family history of congenital anomalies in relatives compared to controls with significant difference in between by using Fisher exact test.

Table 3: Relation between occurrence of different congenital anomalies and risk factors by logistic regression model

Variables	Beta coefficient	P	Odd's (95%CI)
Drug history	0.98	**<0.05**	1.8(0.4-8)
Radiation exposure	0.67	**<0.05**	1.1(1-7.6)
Family history	0.34	**<0.05**	1.01(0.3-4.6)
Consanguinity	0.26	**>0.05**	1(-0.1-5.6)

CI= confidence interval p: p-value

This table shows that drug intake, radiation exposure and family history of congenital anomalies in relatives were considered the most significant independent predictors of congenital anomalies according to binary logistic regression model results.

Table 4: Occurrence & recurrence of congenital anomalies and their relationship with risk factors.

Variables	No	Recurrence		Residence		Age			Med. H.	Drug	Family H.	Consang.
		Same	Other	Rural	Urban	16-25	26-35	35-45				
C.N. S	321	26	61	159	162	114	187	20	33	28	32	81
Head & neck	66	3	5	17	49	12	45	9	0	0	5	9
Thorax	12	0	4	2	10	1	7	4	0	5	0	6
C.V. S	131	16	4	33	98	70	55	6	18	1	31	41
G.I.T & Abd. Wall	50	0	5	16	34	21	24	5	4	4	6	17
Genitor-urinary	139	0	7	48	91	82	48	9	21	17	23	45
Muscle-skeletal	106	29	11	36	70	49	54	3	5	8	9	29
miscellaneous	239	34	31	82	157	110	114	15	47	41	13	77

As shown in table (4), different types of congenital anomalies and the incidence rates & recurrence and their relationship with some threat factors (**fig 1-4**) are tabulated.

CNS anomalies were present in 321 cases. 32 cases with history of occurrence of congenital anomaly in relatives and 81 cases are consanguineous. While, Head & Neck anomalies were present in 66 cases, there were 5 cases with history of occurrence of congenital anomalies in relatives and 9 cases are consanguineous. Regarding, thoracic anomalies were present in 12 cases, and 6 cases are consanguineous. Also, CVS anomalies were present in 131 cases, and 41 cases are consanguineous. Concerning, GIT & abdominal wall anomalies were present in 50 cases, and 17 cases are consanguineous. Moreover, Genito-urinary anomalies were present in 139 cases, and 45 cases are consanguineous. In addition, Musclo-skeletal anomalies were present in 106 cases, and 29 cases are consanguineous. While, Miscellaneous anomalies were present in 239 cases, and 77 cases are consanguineous.

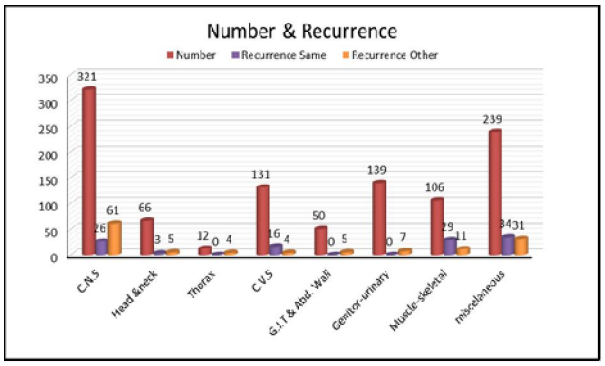

Figure 1: Occurrence & recurrence of congenital anomalies.

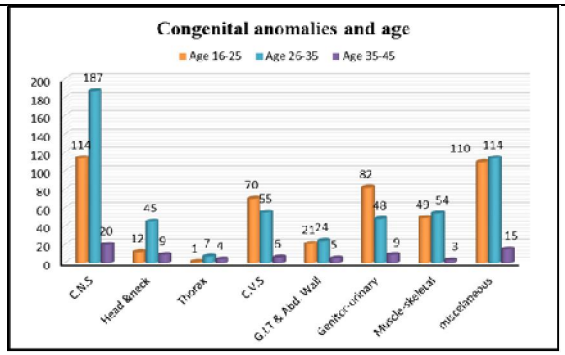

Figure 2: relation between congenital anomalies and maternal age.

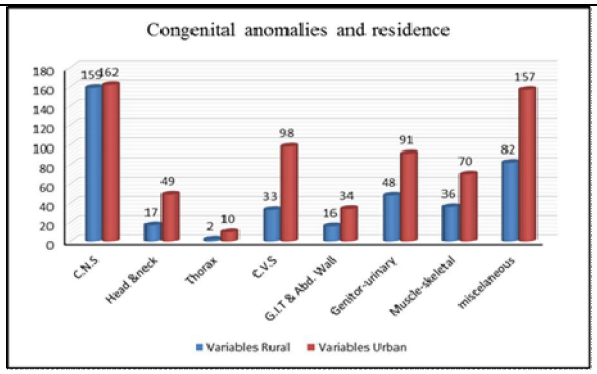

Figure 3: Relation between congenital anomalies and residence.

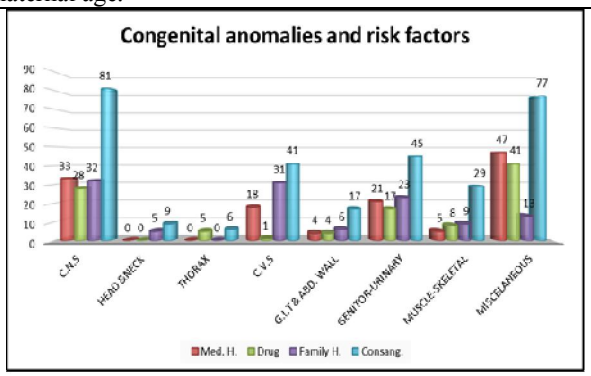

Figure 4: Relation between congenital anomalies and other risk factors.

Table 5: Number & rate of occurrence & recurrence of congenital anomalies

Congenital anomalies	Cases (1000 cases)		Recurrence of same anomaly		occurrence of dissimilar anomaly	
	No	%	No	%	No	%
Neural tube defects	123		5	4.06%	15	12.19%
1. Anencephaly	95	12.3%	5	5.26%	12	12.62%
2. Spina bifida	13	77.24%	0	0%	0	0%
3. encephalocele	15	10.57%	0	0%	3	20%
Hydrocephalus	149	12.19%	14	9.39%	35	23.48%
Dandy walker	28	14.9%	6	21.42%	11	39.28%
Holoprosencephaly	7	2.8%	0	0%	0	0%
Microcephaly	9	0.7%	1	1.11%	0	0%
Absent corpus	5	0.9%	0	0%	0	0%
Cleft lip & palate	61	0.5%	3	4.9%	5	8.19%
Cystic hygroma	5	6.1%	0	0%	0	0%
Multiple cardiac anomalies	93	0.5%	16	17.77%	4	4.44%
Asd	9	9.3% 0.9%	0	0%	0	0%
Vsd	19	1.9%	0	0%	0	0%
Avsd	1	0.1%	0	0%	0	0%
Aortic coarctation	3	0.3%	0	0%	0	0%
Aortic stenosis	1	0.1%	0	0%	0	0%
Echogenic focus	2	0.2%	0	0%	0	0%
Isomerism	2	0.2%	0	0%	0	0%
Transposition of GA	1	0.1%	0	0%	0	0%
Omphalocele	34	3.4%	0	0%	5	14.7%
Gastroschiasis	4	0.4%	0	0%	0	0%
Intestinal Obst.	10	1%	0	0%	0	0%
Intestinal Mass	1	0.1%	0	0%	0	0%
Echogenic bowel	1	0.1%	0	0%	0	0%

This table showed that the number of cases with NTDs was 123 cases; anencephaly represents77.24% with recurrence risk 5.26% and risk of recurrence of dissimilar anomalies 12.62%, Spina bifida represents 10.57% while encephalocele represents 12.19% with recurrence risk of dissimilar anomaly is 20%. Additionally, Number of cases with hydrocephalus was 149 cases with risk of recurrence 9.39% and risk of having another anomaly is 23.48%. while, Number of cases with DWS was 2.8% with risk of recurrence 21.42% and risk of having another anomaly is 39.28%. Number of cases with microcephaly was 0.9% and holoprosencephaly was 0.7% with no recurrence. As well as omphalocele was 3.4%.

4. Discussion:

The current study showed that the mean age of women was 27.1±5 years in group 1 and 26.7±4.5 years in group 2 without significant variation (P>0.05) between or within the two groups with respect to the age. This disagrees with **Bing-Yu *et al.*,** study which reported that the risk factor for appearance of chromosomal and orofacial abnormalities was greater among older ages women **(Bing-Yu *et al.*, 2009).** Additionally, the data revealed that no significant variation was found between the the studied groups with respect to the parity the parity. Other studies reported that nulliparity was associated with an increased risk of specific phenotypes of birth defects **(Hao *et al.*, 2012).**

Also, the results illustrated that no significant variation was noticed between the studied groups with respect to the residence. This study showed that 327 women of cases and 248 women of controls were living in rural areas while 667 of cases and 752 of controls were living in urban areas with insignificant difference (P>0.05). These results disagree with a study which found a significance increase in birth defects among rural residences. **(Waleed *et al.*, 2011).** The reasons for elevation of congenital anomalies among rural residence may be due to persuade for more consanguineous marriage, or increase in the pollution rate which resultant from insecticides and pesticides residues.

Our results indicated that cases had more frequent drug intake during pregnancy compared to controls with statistically significant difference in between. In agreement with our study, there is high risk of fetal malformations if women become pregnant while taking some drugs as antibiotics, NSAIDs, anticoagulants, antidepressants, anticonvulsants and others. Such drugs must be not administered during

gestation and control of pregnancy for a suitable time after stopping of such therapy with these drugs **(March of Dimes Perinatal Data Center, 2001)**. Other studies failed to indicate any significant differences between cases and controls as regard medications during pregnancy **(Saber, 2006)**.

Regarding, cases had more frequent radiation exposure compared to controls with statistically significant difference in between. These results agree with the finding by some researchers who found a correlation exposure pregnant women to x-rays and increased incidence of occurring of Down syndrome and other trisomy's in offspring **(Boue *et al.*, 1975; Creasy *et al.*, 2006).** Our study disagrees with other studies which found no unclear relation **(Kline *et al.*, 2007).** The relationship between the exposure to x-rays during pregnancy and the incidence of occurring of other congenital defects was studied by some researchers, they didn`t report any correlation between the anomalies and exposure to x-rays less than milli sievert (mSv) **(Brent, 2005).** These differences may be due to variability of the dose and type of radiation.

While, cases had more frequent positive history of having birth defects in their relatives compared to controls with significant difference in between. In agreement with our study **Rometti, (2007)** reported that women with a family history of congenital anomalies among one or more of the family members may be highly exposed to a major birth anomalies.

Also, cases had more frequent positive consanguineous compared to controls with significant difference in between. This agrees with several studies which supported consanguinity as an important risk factor for causation of birth defect **(The March of Dimes, 2006).** However, other studies failed to indicate any significance of consanguinity in causation of congenital anomalies **(Saber *et al.*, 2006).**

The number of cases with NTDs was 123 cases; anencephaly represents77.24% (95 cases) with recurrence risk 5.26% (5 cases) and risk of recurrence of dissimilar anomalies 12.62% (12cases), Spina bifida represents 10.57% (13 cases) while encephalocele represents 12.19% (15 cases) with recurrence risk of dissimilar anomaly is 20% (3cases). **American College of Obstetricians and Gynecologists, 2003** reported that anencephaly and spina bifida account for 95% of all neural tube defects and encephalocele accounts for the remaining 5%. In our study, repetition risk of giving delivery to a second child with a neural tube anomalies was 4.06% while it was about 5-10 % in other studies **(American College of Obstetricians and Gynecologists, 2003)**.

Number of cases with hydrocephalus was 149 cases with risk of recurrence 9.39% (14 cases) and risk of having another anomaly is 23.48% (35 cases). Other studies reported that couples who have had one previous child with hydrocephalus have a recurrence risk of 4 **% (Varadi *et al.*, 1988).** A study done by **Olga *et al.*** reported that there was no recurrence of hydrocephalus in next pregnancies but risk of recurrence of dissimilar anomaly was 8.26% **(Olga *et al.*, 2003).** Number of cases with DWS was 28 cases (2.8%) with risk of recurrence 21.42% (6 cases) and risk of having another anomaly is 39.28% (11 cases). Other studies **(Murray *et al.*, 2005)** reported that couples who have had one previous child with DWS, reappearance risk for siblings may be increased when there is a correlation with a single gene deformity. When the data assumed that there is no relationship with a Mendelian or chromosomal deformities then the repetition risk is nearly low (1-5 %)**.**

Number of cases with microcephaly was 9 cases (0.9%) with risk of recurrence 1.11% (1 case) and no risk of having another anomaly. Some studies reported that the pattern of inheritance affects the recurrence for isolated microcephaly whether autosomal dominant or autosomal recessive. 50% recurrence risk rate was reported in the first case where one of the parents is suffered from defects, while 25% recurrence risk rate appeared in the second case where the microcephaly is due to an aneuploidy, such as trisomy 21, the reappearance risk is approximately 1% in addition to the maternal-age-related risk. If the microcephaly is due to a deletion or rearrangement in the chromosomes, parental karyotyping should be performed to rule out a balanced translocation, which would increase the recurrence risk. If microcephaly is secondary to drug exposure or infection, the recurrence risk is expected to be minimal in a subsequent pregnancy **(Tolmie *et al.*, 2007).** These differences in results are due to the underlying cause of microcephaly.

Number of cases with holoprosencephaly was 7 cases (0.7%) with no recurrence. Other studies reported that recurrence risk is 20% for parents whose fetus had holoprosencephaly and a normal karyotype **(Zipursky *et al.*, 2014).** Number of cases with cleft lip & palate was 61 cases (6.1%) with risk of recurrence 4.9% (3 cases) and risk of having another anomaly is 8.19% (5 cases). **Arosarena (2007)** reported that reappearance risks are correlated with the type; for example in case of cleft lip and palate there is no increased risk for isolated cleft palate and vice versa**.** Reappearance risk is based on family history, the presence or absence of other physical or cognitive character within a family, and prenatal exposure. **Olga *et al.*,** study found that risk of recurrence of cleft lip & palate was 2.7% while risk of having dissimilar anomaly was 2.78% **(Olga *et al.*, 2003).** Number of cases with omphalocele was 34 cases (3.4%) with no recurrence but risk of having another anomaly is 14.7% (5 cases). Other studies reported that couples

who have had one previous child with, risk of recurrence less than 1**% (Romero *et al.*, 2010).**

Conclusions

Cytogenetic analysis and genetic therapy are available nowadays for pre- pregnancy planning and pregnancy. A pregnant woman should avoid smoking, unnecessary medications and exposure to chemicals & radiations to increase the chance of having a healthy baby. Application of regular examination using recent models of ultrasound early in gestation can detect accurately the gestational age, multiple pregnancies and detect early any foetal malformation and support the decision of pregnancy termination. Therefore, the profit for other substantive outcomes are less clear.

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