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Risk of Subsequent Miscarriage Increases after Each Miscarriage in Patient visiting Shree Bhawani Hospital and Research Center

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Abstract: ***Subsequent miscarriage have an increased future risk of miscarriage .The purpose of the study was to find out whether subsequent miscarriage is a risk factor for further miscarriage or not. Case control was the method of study where the source of case was hospitalised patients with subsequent miscarriage and the source of control was general population. Simple random technique was used as method of sampling in which certain patients with subsequent miscarriage (20-30 years) age group were taken under the study. The sample size was 35 and odd ratio was used for the estimation of risk of disease associated with exposure. Subsequent miscarriage showed a risk of having further miscarriage 3.3 times than that of nulliparous women. Thus subsequent miscarriage can be considered as a major risk factor for future miscarriage.***

Keywords: Miscarriage, risk factor, subsequent miscarriage

1. Introduction

Miscarriage is defined as the spontaneous loss of pregnancy before the fetus reaches viability. It includes all pregnancy losses from the time of conception until 24 weeks of gestation. Recurrent miscarriage may be defined as three or more consecutive first trimester miscarriage or one or more second trimester miscarriage. Recurrent miscarriage affects 1% of couples trying to conceive. It has been estimated that 1-2% of second trimester pregnancies miscarry before 24 weeks of gestation.

Risk factors for recurrent miscarriage:

(a)Epidemiological factors:
Maternal age and number of previous miscarriage are two independent risk factors for a further miscarriage. Age related risk of miscarriage can be described as below:
12-19yrs: 13%
20-24yrs: 11%
25-29yrs: 12%
30-34yrs: 15%
35-39yrs: 25%
40-44yrs: 51%
>45yrs: 93%

Previous reproductive history is an independent predictor of further pregnancy outcome. The risk of further miscarriage increases after each successive pregnancy loss, reaching approximately 40% after three consecutive pregnancy losses and the pregnancy worsens with increasing maternal age. A previous live birth does not preclude a woman developing recurrent miscarriage. Maternal cigarette smoking and caffeine consumption have been associated with increased risk of spontaneous miscarriage in a dose dependent manner. However current evidence is insufficient to confirm this association. Heavy alcohol consumption is toxic to embryo and the foetus. Even moderate consumption of five or more units per week may increase the risk of sporadic miscarriage. Recent retrospective studies have reported that obesity increases the risk of both sporadic and recurrent miscarriage.

(b)Antiphospholipid syndrome:
It is the most important treatable cause of recurrent miscarriage. It refers to the association between antiphospholipid antibodies-lupus anticoagulant, anticardiolipin antibodies, and anti-B2 glycoprotein-1 antibodies and adverse pregnancy outcome or vascular thrombosis. The mechanism by which antiphospholipid antibodies cause pregnancy morbidity include inhibition of trophoblastic function and differentiation, activation of complement pathways at the maternal fetal interface resulting in a local inflammatory response and in later pregnancy, thrombosis of the uteroplacental vasculature. Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage.

(c) Parental chromosomal rearrangements
In approximately 2-5% of couples with recurrent miscarriage, one of the partners carries a balanced structural chromosomal anomaly: most commonly a balanced reciprocal or Robertsonian translocation. Although carriers of a balanced translocation are usually phenotypically normal, their pregnancies are at increased risk of miscarriage and may result in a live birth with multiple congenital malformation and /or mental disability secondary to an unbalanced chromosomal arrangement.

(d) Embryonic chromosomal abnormalities:
In couple with recurrent miscarriage, chromosomal abnormalities of the embryo account for 30-57% of further miscarriage. Its risk increases with advanced maternal age. As the number of miscarriage increases, the risk of euploid pregnancy loss increases.

(e) Congenital uterine malformation:
The reported prevalence of uterine anomalies in recurrent miscarriage population ranges between 1.8% and 37.6%. Its

prevalence is higher in second trimester compared to first trimester. An arcuate uterus tends to miscarry in second trimester whereas septate uteri are more likely to miscarry in first trimester.

(f) Cervical weakness:
Contribute second trimester miscarriage.

(g) Endocrine factor:
Diabetes mellitus and thyroid disorder contribute to the recurrent miscarriage. A diabetic woman with high HbA1c in first trimester is associated with miscarriage and fetal malformation. Antithyroid antibodies have been linked to recurrent miscarriage.

(h) Immune factors:
HLA incompatibility between couples, the absence of maternal leucocytotoxic antibodies or the absence of maternal blocking antibodies, altered peripheral blood NK cells, cytokines do not contribute to recurrent miscarriage so should not be part of routine investigations.

(i) Infective agents:
Any severe infection that causes bacteremia or viraemia lead to recurrent miscarriage. The presence of bacterial vaginosis in first trimester has been reported as a risk factor for second trimester miscarriage and preterm delivery.

(j) Inherited thrombophilic defects:
Inherited thrombophilias have been implicated as a possible cause in recurrent miscarriage and late pregnancy complications with the presumed mechanism being thrombosis of the uteroplacental circulation. The association between thrombophilias and late pregnancy loss has been consistantly stronger than for early pregnancy loss.

Investigations:
a) **Antiphospholipid antibodies:** For both first and second trimester.
b) **Karyotyping:** Cytogenetic analysis should be performed on product of conception of the third and subsequent consecutive miscarriages. If the karyotype of the miscarried pregnancy is abnormal, there is a better prognosis for the next pregnancy.
c) **Anatomical factors:** All women with recurrent first trimester miscarriage and all women with one or more second trimester miscarriages should have a pelvic ultrasound to assess uterine anatomy.
d) **Thrombophilias:** Women with second trimester miscarriage should be screened for inherited thrombophilias including factor v Leiden, factor 2 (prothrombin) gene mutations and protein s.

Treatment options for recurrent miscarriage:
a) **Antiphospholipid syndrome:** Pregnant women with antiphospholipid syndrome should be considered for treatment with low dose aspirin plus heparin to prevent further miscarriage.
b) **Genetic factor:** The finding of an abnormal parental karyotype should prompt referral to a clinical geneticist. Pre-implantation genetic screening with in vitro fertilisation treatment in women with unexplained recurrent miscarriage does not improve live birth rates.
c) **Congenital uterine malformation:** There is insufficient evidence to assess the effect of uterine septum resection in women with recurrent miscarriage and uterine septum to prevent further miscarriage.
d) **Cervical weakness and cervical cerclage:** In women with a singleton pregnancy and a history of one second trimester miscarriage attributable to cervical factors, an ultrasound indicated cerclage should be offered if a cervical length of 25 mm or less is detected by transvaginal scan before 24 weeks of gestation.
e) **Endorine factors:** Diabetes and thyroid disorder should be kept under consideration for proper treatment.
f) Immunotherapy
g) **Inherited thrombophilias:** Heparin therapy during pregnancy may improve the live birth rate of women with second trimester miscarriage associated with inherited thrombophilias.
h) **Unexplained recurrent miscarriage:** Women with unexplained recurrent miscarriage have an excellent prognosis for future pregnancy outcome without pharmacological intervention if offered supportive care alone in setting of a dedicated early pregnancy assessment unit.

2. Methodology

Case control was the method of study where the source of case was hospitalised patients with miscarriage and the source of control was general population. Simple random technique was the method of sampling. Odd ratio was used for the estimation of risk of disease associated with exposure. After data was collected from the survey, we found that 60 patients had miscarriage. The population mean is within 10 unit interval that is 60+/- 10. Assuming that the distribution of the sample was approximately normal, the following formula was used to calculate the size of the sample: Z2 S2/d2 where N=size of the sample, Z= Z statistics for desired level of confidence. s= population standard deviation, d= half width of desired interval. For 95% confidence, Z= 1.96, let the interval be 50-70, so d=10. Assuming standard deviation to be 30. Using above formula, we get sample size to be 35.

3. Result

(a) Exposure rate among the cases and control.

	Cases (with miscarriage)	Control (without miscarriage)
Subsequent miscarriages >3	a=15	b=20
Nulliparous	C=2	d=5
Total	(a+c)=17	(b+d)=25

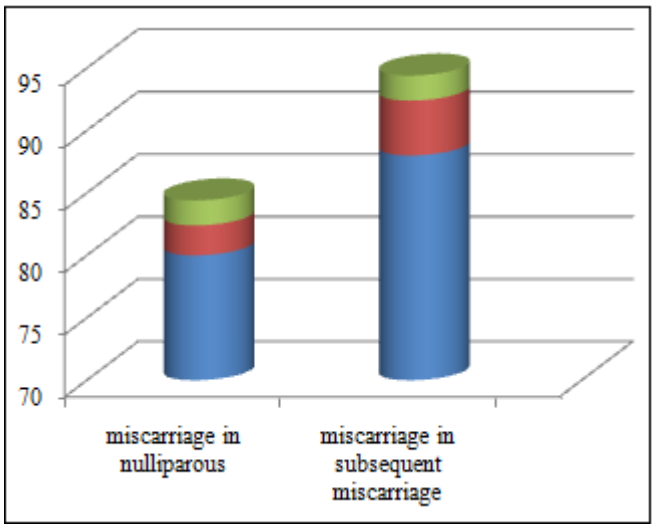
Exposure rate among cases= a/ (a+c) = (15/17) x100 = 88.2%
Exposure rate among control = b/ (b+d) = (20/25) x100 = 80%
So the frequency rate of miscarriage is definitely higher among patients with previous miscarriages than that in nulliparous.
P value is less than 0.5 so the null hypothesis can be neglected and alternate hypothesis 'Risk of subsequent

miscarriage increases after each miscarriage' can be accepted.

(b)Estimation of disease risk associated with exposure (odd ratio).

	Miscarriage (yes)	Miscarriage (no)
Exposed (subsequent miscarriage)	a =20	b =15
Non exposed(nulliparous)	c =2	d =5

Odd ratio = ad / bc = 20x5 /15x2 =3.3
Thus subsequent miscarriage showed a risk of having further miscarriage 3.3 times than that of nulliparous.



Number of previous miscarriage	Number of patient with recent miscarriage
0	2
1	2
2	8
3	10
4	13

Fig: previous miscarriages causes increase in risk for future miscarriage.

4. Discussion

A successful pregnancy requires an optimal interplay between the maternal immune system and the semi-allogenic fetus. Breakdown of the maternal immune tolerance may result in the fetal rejection. Thus the maternal tolerance toward the fetus has to be maintained both locally at the fetal-maternal interface and systemically, since bidirectional trafficking of cells and soluble HLA between the mother and the fetus takes place [1]. Globally, an estimated 23 million miscarriages occur every year, despite the personal toll involved, many miscarriages- defined as the loss of pregnancy before viability- are managed in relative isolation. Private grief and misconceotions-eg, the belief that miscarriage can be caused by lifting heavy objects, or that there are no effective treatments- can lead to women and their partners feeling at fault or managing alone. Similarly, in the health –care system and broader society, the continuing conviction that miscarriages are unavailable and the requirement, enshrined in many national guidelines, that women must have recurrent miscarriages before they are eligible for investigation or intervention has created a pervasive attitude of acceptance of miscarriage, urging women to 'just try again'. This mindset underestimates, and risks dismissing, the personal physical and mental consequences of a miscarriage [2]. According to a research, on the live database, 716 consecutive patents were entered with a history of recurrent miscarriage and 325 of these were identified as having 'idiopathic recurrent miscarriage'. 23 of whom were lost to follow-up. Following postnatal contact, 76 patients reported no further pregnancy. Of the remainder, 70% subsequently achieved a further pregnancy, two of which were found to be ectopic, and two patients had termination of pregnancy [3]. Emotional distress and other mental health conditions have been associated with pregnancy loss, less is known about mental health impact of these events during subsequent pregnancies and births [4]. According to a research, miscarriage are common among parous women, 43% of parous women report having experienced one or more first trimester spontaneous miscarriage, rising to 81% among women with 11 or more living children. One in every 17 parous women have three or more miscarriage. Depending on her health, nutrition, and lifestyle choices, even a 39 years old parous women with a history of 3 or more miscarriage has a good chance of carrying a future pregnancy to term but she should act axpediently[5]. Over 70% of women who miscarry in their first pregnancy are desired to carry a subsequent pregnancy beyond 24 weeks. However, as yet relatively little is known about the potential complications in this second pregnancy. The risks of preterm birth and perinatal death were increased in women with a previous miscarriage and were markedly higher in case of late miscarriage [6]. The language of miscarriage should be respectful, oriented to the meaning the miscarriage has for the women experiencing it, and consistent across all persons providing care. When one considers the enormity of early pregnancy loss and its effect on up to 1 million women and their families each year in the United States, research, quality initiatives, relationship-based clinical practice, and precise language are imperatives [7]. A research indicated that there are six super ordinate themes in relation to the participants experience of miscarriage: acknowledgement of miscarriage as a valid loss, misperception of miscarriage, the hospital environment, management of miscarriage , support and coping, reproductive history and implications for future pregnancies[8]. Secondary infertility is a feature of recurrent miscarriage. Embryonic vital signs in preceding pregnancies are prognostic markers and should be regarded as a strong confounding factor in trials on therapeutic interventions. Prevention may be more appropriate than treatment [9].

5. Conclusion

Subsequent miscarriage increases the risk of further miscarriage. Miscarriage is rapidly becoming a global public health crisis with subsequent miscarriage being recognised as its most important causative factor.

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