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REVIEW

What about superfertility, decidualization, and natural selection?

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Recurrent pregnancy loss, defined as two or more failed pregnancies by the American Society for Reproductive Medicine [1], is a clinical problem because known effective treatment is limited. Effective treatment depends on the cause of the reproductive failure. Thus, attention has been focused on determining causes of recurrent pregnancy loss. Even so, to date, only chromosomal abnormalities of the conceptus and immunologic risk factors have been generally accepted as etiologies of recurrent pregnancy loss. Recently, a novel pathologic pathway that involves impaired decidualization of endometrial stromal cells has been proposed as a cause of recurrent pregnancy loss [2]. Further, it has been hypothesized that the impaired decidualization is manifested by the prolongation of the window of implantation allowing for increased fecundity and "superfertility" [2–7]. The following paragraphs will describe the evidence for these notions.

Decidualization

Decidualization of the endometrium is essential for successful implantation of all species in which the blastocyst breaches the uterine epithelium [8]. It is characterized by secretory transformation of the uterine glands, influx of specialized uterine natural killer cells, vascular remodeling, and morphologic and biochemical reprogramming of the endometrial stromal cells. Major secretory products of decidual stromal cells include prolactin and insulin-like growth factor binding protein-1 (IGFBP-1), two proteins that have been used as markers of decidualization [9]. In humans, decidualization begins approximately 6 days after ovulation at the onset of the putative window of implantation which is thought to last not more than 2–4 days [10]. One effect of abnormal decidualization has been postulated to result in a prolongation of the window of implantation [2–7]. Biochemical support for this concept is provided by studies of cultured endometrial stromal cells from women experiencing recurrent miscarriage both in vitro and in vivo [3]. Analyses of midsecretory endometrial biopsies from women with and without a history of recurrent pregnancy loss demonstrated that recurrent pregnancy loss is associated with decreased expression of the decidual marker prolactin and an increased expression of prokinectin-1, a cytokine that promotes implantation [3]. These in vivo findings were confirmed in vitro when endometrial stromal cells from women with and without recurrent miscarriages were decidualized in culture [3]. These co-culture experiments provided evidence that impaired decidualization prolonged the window of implantation [4]. The consequences of prolonged window of receptivity would be expected to (1) facilitate delayed implantation of compromised embryos and (2) increase fertility or the probability of achieving pregnancy within one menstrual cycle.

Capsule It is becoming increasingly apparent that the causes of recurrent pregnancy failure go well beyond previously held notions of embryo chromosome abnormalities when viewed in the context of natural selection rather than the consequences of human ART treatments.

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Fertility

Fertility rates can be measured as the time taken to achieve pregnancy expressed as monthly fecundity rates (MFRs), that is, the probability of achieving pregnancy within one

menstrual cycle [11]. While age dependent, the average MFR in humans has been reported as 20 %, moderate and severe infertility as MFR of 5 and 1 %, respectively, and superfertility as MFR of 60 % or greater [11]. Using a mathematical model, it has been estimated that 79 % of the population is fertile, 18 % subfertile, and 3 % superfertile [11, 12]. Using the model of Tietze [12], two studies have shown that 32–40 % of women experiencing recurrent pregnancy loss are superfertile [3, 13]. When the 32–40 % prevalence of superfertility among women with a history of recurrent pregnancy loss was compared with the 3 % prevalence in the general population [11, 12], the difference was significant ($P < 0.0001$) [13]. Confirmation of the association of superfertility and recurrent pregnancy loss adds clinical support to the concept that impaired decidualization resulting in prolongation of the window of implantation is a cause for recurrent miscarriages. Prolongation of the window of implantation could lead to implantation of developmentally delayed or compromised embryos.

Karyotype of products of conception

The most common abnormality found in developmentally compromised preimplantation embryos as well as aborted products of conception is an abnormal chromosome complement [14–16]. A recent study of products of conception from 200 women experiencing recurrent miscarriages revealed a 20 % chromosomal abnormality rate [13]. When this study was expanded to look at results of 309 karyotypes from 420 women with a history of recurrent miscarriage, 25 % (78/309) displayed abnormal chromosome complement and 75 % (231/309) were normal [14]. Among the 231 normal karyotypes, 53 % (121/231) were 46,XX and 47 % (109/231) were 46,XY suggesting that the high rate of chromosomal normality was not in large part explained by maternal contamination [13, 14]. Results of chromosome analysis from abortus material from women experiencing recurrent miscarriages reported in the literature are shown in Table 1. Aneuploidy rates have varied from 20 to 78 % [13–23]. All reports of aneuploidy rates greater than 30 % were obtained from a population of abortuses sent to the chromosome analysis laboratories [15, 16, 18] in contrast to those obtained from a population of recurrent aborting women [13, 14, 17, 19]. If the prevalence of abnormal concepti among women with a history of recurrent pregnancy loss is the question, then the population women of recurrently aborting must be studied rather than the products of conception. Investigating the products of conception for obstetrical history of the women who aborted will provide information regarding the sensitivity and specificity. One of the highest chromosomal abnormality rates observed when comparative genomic hybridization (CGH) was used for the analysis rather than cytogenetics [23]. The explanation for increased abnormality rate given was the fact that CGH can detect microdeletions and microduplications across the genome [23]. The problem with this explanation is that the frequencies of these microdeletions among embryos resulting in live birth are not known. Recurrent aneuploidy occurred in 10 % (19) and 14 % (data not shown) of patients experiencing recurrent pregnancy loss who had two or more miscarriages karyotyped. When comparing the frequencies of all karyotypes of products of conception from women with a history of recurrent pregnancy loss with those reported from all spontaneous abortions [24, 25], a significant difference ($P < 0.0001$) is observed.

Thus, the contribution of abnormal concepti as a cause of recurrent pregnancy loss may have to be reassessed. While an abnormal chromosome complement of the conceptus has been accepted as the most common cause for all miscarriages, uterine causes have accounted for almost half of all miscarriages [26].

Table 1 Results of chromosome analysis from abortus material from women experiencing recurrent miscarriage

Study	Number	Mean age (year)	% Abnormal karyotype POC
Stern [15]	224	35	57
Ogasawara [16]	234	31	51
Carp [17]	125	32	29
Stephenson [18]	420	34	46
Sullivan [19]	255	31	25
Marquard [20]	137	39	78
Grande [21]	376	35	60
Sugiura-Ogasawara [22]	482	32	41
Robberect [23] CGH	51	–	66
Orlando [13]	192	35	20
Coulam [14]	420	35	25

Conclusion

Recurrent pregnancy loss is associated with impaired decidualization leading to a significantly higher prevalence of superfertility than the normal population. Abortuses from women with a history of recurrent pregnancy loss display a higher prevalence of chromosomally normal pregnancy losses compared with sporadic abortions. It had been proposed that in view of the high incidence of gross chromosomal errors in human preimplantation embryos, decidualization is a means of natural selection of embryos limiting maternal investment of impaired pregnancies [2–7]. If our data can be confirmed, natural selection of embryos for implantation would have to

include embryos developmentally compromised for reasons other than chromosomal abnormalities.

By restricting the window of implantation, the continuously changing endometrial environment is aligned to meet the requirements of an implanting blastocyst. Prolonged endometrial receptivity carries a risk of implantation of developmentally delayed embryos thus facilitating non-synchronized embryo implantation in an unsupportive environment. In addition, asynchrony between endometrial and embryo development in early pregnancy may trigger a spectrum of pathological events, leading to miscarriage or predispose for obstetrical complications associated with defective placentation, such as preeclampsia, fetal growth restriction, and preterm birth [27].

Decidualization has also been suggested as a means of providing natural selection of embryos to limit maternal investment of impaired pregnancies [2–7]. Co-culture experiments have shown that decidual cells sense signals from developmentally compromised embryos and respond by shutting down the secretion of cytokines necessary for implantation [2]. Delayed implantation could negate embryo quality control and cause early placental failure, regardless of the embryonic karyotype. This pathological pathway provides an explanation for the observation that some patients experiencing recurrent pregnancy loss seem exceptionally fertile, often conceiving within one or two cycles. Thus, as the clinical correlate of inappropriate uterine receptivity, "superfertility" should be considered as a genuine reproductive disorder that requires targeted intervention. However, little information is available regarding the molecules that signal closure of the window of implantation [28]. The expression of a gene of the TGF family called endometrial bleeding associated factor (ebaf) has been identified only in late secretory and not in the proliferative, early, or midsecretory phases of the menstrual cycle [29]. In situ hybridization revealed the expression was primarily confined to mesenchymal cells of the endometrial stroma rather than the epithelium or endothelium [29]. Ebaf was shown to be prematurely increased during the window of implantation in a subset of infertile patients and its overexpression to inhibit the expression of IGFBP-1 and prolactin, key decidual proteins [30]. Whether under expression of ebaf results in prolongation of the window of implantation requires further study.

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