REVIEW

Lowering the Premature Birth Rate: What the U.S. Experience Means for Japan

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Abstract: Premature birth rate and low birth weight rate are increasing in industrialized countries including USA and Japan. The Infant mortality rate (IMR) is three times and 50-75 times greater for infants born at 32-36 weeks and <32 weeks respectively than term-born counterparts. In the U.S., the IMR is greater than in Japan particularly among black infants and simply the "lower socioeconomic class" is not the answer. Premature birth is heterogeneous in origin and idiopathic in 70% of the cases. Increased utilization of assisted reproductive technology only accounts for a part of the recent trend. Evidence suggests environmental factors play a significant role, and genetic-environmental interaction is plausible. A chronic psychosocial stress of pregnant women has been postulated to be modifying the endocrine milieu thereby influencing pregnancy outcomes. In a preliminary observation in St. Louis, homeless pregnant women with high behavioral and social risks, when accommodated in a shelter home designed for these women, produced significantly less numbers of premature and low birth weight infants as compared with the general population. Furthermore, in a randomized controlled study in Washington DC, psychobehavioral intervention specifically targeting smoking (primary and secondary), intimate partner violence (IPV), and depression among black pregnant women significantly decreased the rate of miscarriage and low birth weight. These reports may have significant implication to the Japanese situation. Increasing number of Japanese women at reproductive age are exposed to smoking, may have underling psychosocial stress and may suffer from subclinical depression and/or from IPV. Detailed epidemiological studies of women before and during the reproductive age with regard to risk factors can lead to an effective intervention strategy against premature birth in Japan. (Keio J Med 57 (1) : 45–49, March 2008)

Key words: Premature birth, Low birth weight, United States, Japan, Intervention

While the survival rate of premature infants has been improving remarkably in the past few decades thanks to the progress in maternal fetal medicine and neonatology, premature birth and low birth weight (LBW) still is a significant issue associated with higher mortality and morbidity compared with that of full term newborns. Moreover, a challenge is the increasing rate of premature and LBW births in developed countries,[1,4] including Japan where the premature birth rate rose from 4.2 % to 5.6% and LBW rate rose from 5.6 to 9.4% between 1980 and 2004.[5] LBW is defined as birth weight <2500 g and includes many premature and all the small for gestation infants. Since birth weight is often the most accurate and readily available parameter, LBW is used instead of prematurity in many retrospective reports. The infant mortality rate (IMR) is three times and 50-75 times greater for 32-36 week and less than 32 week gestational age infants respectively compared with that for term infants. Among the survivors, morbidity is likewise greater, the less mature they are. Relatively mild premature infants

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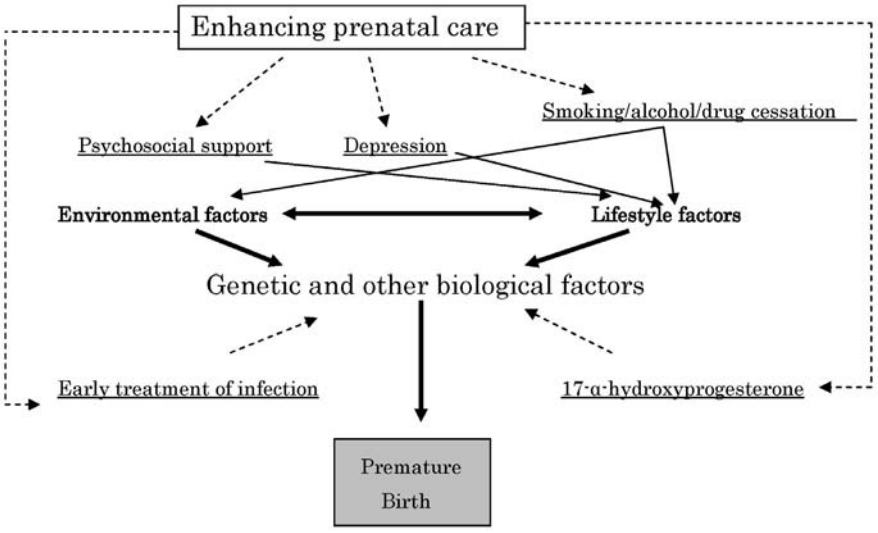

Fig. Schematic model of interventions for premature birth. Premature birth is directly related to biological process of premature uterine contraction. This biological process is influenced by environmental and lifestyle factors that interact to each other. Interventions target this process and examples of intervention are demonstrated by dotted arrows. Enhancing prenatal care is designed to identify women early who may benefit from medical interventions such as treatment of infections or hormonal therapy, and provides personalized psychosocial support, specific education, linking to necessary services etc..

at 33-38 week are nowadays expected to survive over 99%, and the majority of them develop and perform well at school age. However, as a subpopulation of newborns, those mild degree premature infants are still at a higher risk for cognitive deficit and learning disabilities compared with full term counterparts and account for 70% of prematurity-associated developmental deficit that burdens not only the individual and family but also the community they live in.[6,7] Since 1970s in the United States, there have been governmental and non-governmental activities to counteract this problem by campaigning to improve the rate of prenatal care for pregnant women, installing the Prematurity Prevention Committee by the Institute of Medicine, inaugurating the NIH Prematurity Prevention Research Meeting, and authorizing reimbursement for prenatal care by Medicaid (a national insurance program). However, the impact of these activities in the real world is yet to be seen. As the mechanism of labor is not well understood, it is likely that the premature birth and LBW will be with us for awhile.

In the United States, the IMR is higher than that of Japan and the leading cause of infant mortality is congenital birth defects followed by prematurity and LBW.[1] If all the disease conditions associated with prematurity and LBW are bundled together, the prematurity-related IMR equals with that due to congenital defects. An important fact with regard to infantile mortality in the United States is health disparities among the race/ethnic groups. Although this point may sound irrelevant to the Japanese situation, studying the phenomenon can lead to better understanding of premature birth in general. The IMR gap between black and white infants has not been narrowing over the past few decades.[8] This is almost in parallel to the gap of LBW rates between the two populations. The other minority group, Hispanic, has the IMR similar to whites. This black vs. Hispanic difference seems to indicate that the high IMR among black infants is not simply related to the poor social and economical status per se, since they are both lower and similar compared with whites. Though the offspring of college educated black parents had better figures in the mean birth weight, premature birth rate and LBW birth rate than those of the non-college educated black parents, the rates were still 2-3 times higher than the offspring of white college educated parents.[9] Interestingly, the first generation Asian Indians living in California are in general well educated and in the higher socioeconomic class and yet their offspring had a higher risk for low birth weight comparable to blacks,[10] again suggesting socioeconomic class is not the determinant of the LBW rate difference among race/ethnic groups. Do these data support genetic factors for prematurity and LBW then? Not entirely. There is a retrospective study looking at birth weight over three generations longitudinally among different cultural/ethnic backgrounds from 1956.[11] In this study, there was no difference between the mean birth weight of female infants born to white European new immigrants (first generation) and those to the contemporary American white residents. The female infants (second generation) born to the first generation women showed again no difference in the birth weight between the two groups nor at the third generation level. The birth weight

stayed the same over the generations. In contrast, when the female black offspring of newly immigrated from African or Caribbean countries were compared with those from contemporary American black residents, the birth weight was significantly greater and LBW rate was lower among the new immigrants at the second generation level. At the third generation level, however, these advantages in the new immigrant group had been lost. The LBW rate rose and the birth weight declined comparable to that of the American black resident group. Similar observations have been made in the Mexican immigrants to the U.S. where the birth weight of the first generation was greater than that of the second generation.[12] These studies indicate either acculturation in America, or living in an industrialized modern society over generations could negatively influence on the process of pregnancy and parturition process of these minority populations.

When the birth weight-specific infant mortality rates were examined, the IMR is lower among blacks compared with whites if a birth weight is less than 2000 g, e.g. a black infant with a birth weight 1 kg has a better chance of living compared with a white infant of the same birth weight and gender. It is clear that the higher IMR among blacks in the U.S. is not due to their individual higher mortality but rather to their higher rate of LBW birth rate. Again we face the question of why the higher LBW rate persists among blacks. Sociologists, public health researchers, obstetricians and pediatricians predict that it will take some time to find the cause of this problem. The causes of premature and LBW birth are variable and different in each case. Some are known such as fetal distress, abruptio placenta, pregnancy induced hypertension which necessitate delivery of the fetus to protect the mother and/or fetus, but majority of premature births are associated with no known causes. Williams Obstetrics states that the spontaneous (idiopathic) variety makes up 72% of all premature births.[13] Among the heterogeneous group of the so called 'idiopathic' premature deliveries, there are often associated risk factors with premature labor. Such risk factors include 1. Positive history of previous premature delivery, 2. Teenage pregnancy, 3. Short inter-pregnancy period, 4. Smoking and 5. Psychosocial stress.

Positive history of previous premature delivery : If the previous pregnancy resulted in singleton delivery at gestation 29-32 weeks, the odds of producing <35 premature infant in the subsequent delivery is 10 times higher compared with a case where the previous delivery was ≥35 weeks. The odds ratio increases to 12.5 times if the previous delivery was 29-32 weeks gestation.[14]

Teen age pregnancy: Birth rates for premature infant and LBW are higher for teenage women. The risk is highest if the mother is 14 years old or younger. However, the total number of premature births born to the women of this age group in the U.S. is relatively small.[15] The number of total premature infants born to the 15-19 year age group is higher and so is the social impact.

Short pregnancy interval: It is intuitively accepted that the uterus needs an adequate recuperating period before the next pregnancy. Indeed the risk of preterm or LBW delivery is significantly higher among the blacks if the interval is less than 6 months. Similar phenomena are observed for whites also when the interval is only 3 months.[16]

Smoking: There are a few theories to explain the association between smoking exposure and low birth weight. To have the best outcome of pregnancy, the condition of the women's body should be prepared best for carrying a fetus. The vasoconstrictive and other adverse effects of nicotine and other substances in tobacco are considered counteractive. Evidence is accumulating to indicate that even second handed smoking is hazardous to pregnancy.[17]

Psychosocial stress: This is an intense area of investigation in relation to premature and LBW delivery. Cooper *et al*. demonstrated in a prospective study that maternal education level and the degree of stress determined by a scoring system were associated with a higher premature birth rate.[18] College educated black parents experienced a greater incidence of premature infants than their white counterparts, as I quoted above. Those data can be interpreted in this psycho stress model as black couples expending more family resources than white families. They could have been exposed to greater stress to attain the same level of life style, negatively impacting on the pregnancy outcomes. Biological functions age with stress like body function wears down when it is exposed to harsh weather conditions for a long period of time. This 'weathering hypothesis' states that long term unconscious stress ages the body function through the endocrine mechanisms by changing pituitary-adrenal and pituitary-gonad axis which then directly and/or indirectly affects the pregnancy states and parturition mechanism.[19] If this is true, an intervention strategy can be constructed accordingly.

Experience in the United States: The figure outlines possible biological and environmental factors contributing to LBW/premature births and areas of intervention. Known causes of premature births sometimes can be intervened such as with 17-α-hydroxyprogesterone for women with recurrent miscarriages/premature births or treatment of infection during pregnancy. For those women with 'idiopathic' premature labor, no preventive measure has been instituted in a large scale systematically. Thus the impact of an intervention on the birth outcomes in a community has not been tested. Olds has shown that professionally trained nurse visits to underserved pregnant women was effective in improving the birth weight average compared with home visits by specially trained lay persons.[20] The concept of this intervention is incor-

Table 1. Premature and LBW rates among infants born to homeless women at the Our Lady's Inn, a shelter home in St. Louis.

	<2500 g	<37 weeks
St. Louis City*		
Black	14.7	22.9
White	7.4	13.1
All races	11.9	19.2
National§		
Black	13.7	17.9
White	7.2	11.5
All races	8.1	12.5
St. Louis shelter home		
	9.7	9.7†

The 123 homeless women admitted to the shelter home from 2003 to 2006 and whose infants' birth weight was available were analyzed. None of the maternal characteristics differed from those women whose infants' birth weight was not available (not shown). Eighty percent of the women were black. *:2003–2006 cumulative data from Missouri Department of Health and Senior Services, §:2004 data from National Center for Health Statistics. †: different compared with St. Louis black or all races $p<0.01$.

Table 2. Birth outcomes in the integrated psycho-behavioral intervention group compared with the usual care (control) group in Washington DC.

Pregnancy outcomes	Intervention (n=430)	Usual care (n=441)	p-value
Miscarriage	1.4%	4.8%	0.04
Premature <37 week	12.6	14.3	0.53
Premature <34 week	2.0	5.4	0.15
LBW <2500 g	12.2	14.1	0.45
VLBW <1500 g	0.6	2.8	0.03

Pregnant black women (n=1044) with at least one of the four 'risk factors'-- smoking, secondary smoking (environmental tobacco exposure), victim of intimate partner violence and depression-- were randomly assigned to either integrated intervention counseling or usual care group. The intervention is composed of maximum 8 counseling sessions during the pregnancy. The figures are from the reference 24.

porated in 'Enhancing Prenatal Care' in the figure describing possible areas for intervention. Enhancing prenatal care here includes: Better collection of information from women particularly with regard to lifestyle, systematic and tailored instruction/communication at appropriate intervals, timely linking to necessary services and agencies where indicated, etc.. In the city of St. Louis in the Missouri State, USA, there are 3 shelter homes for pregnant women. Those women are 84% black women, associated various high risk lifestyle factors including drug addiction (42%), history of sexually transmitted diseases (35%), victims of domestic violence (46%), victims of sexual abuse (31%) and victims of incest (13%). Sheltered pregnant women are in general associated with higher premature birth and LBW rates compared with the same socioeconomic and ethnic/cultural counter parts.[21,22] We have examined the birth weight of newborn infants born at one shelter home since 2003.[23] Some of the women left the shelter home and information was not available. For those whose infant's birth weight is known, the premature birth rate showed a better trend than the city and the national averages despite adverse life conditions (Table 1). This shelter home provides free food and board, nursing care and mental health care when indicated. Though this is a preliminary observation, the result is encouraging and supports the Olds' theory that assistance by professional personnel of indigent pregnant women produces a better birth weight outcome for even highly stressed women. In Washington, DC, El-Mohandes *et al.* recently conducted a prospective randomized controlled study (RCT) where nearly 3000 high risk black pregnant women were recruited and 1044 eligible individuals were studied (Table 2).[24] The intervention group was provided with educational and counseling sessions by trained black professionals up to 8 times during the pregnancy period specifically targeting primary smoking, secondary smoking, intimate partner violence and depression. Many of the women had more than one of these risk factors. For various reasons, the sessions were given to the participants variably 1-8 times because of the participants' conditions. Nonetheless, the intervention group was associated with significantly low miscarriage and low birth weight rates compared with the control group. The importance of the study is that they identified that at least four specific elements can be targeted in a larger scale.

Application to Japan: Japanese IMR is one of the lowest in the world and the premature birth and LBW rates are significantly lower than the U.S. Japanese people are relatively homogeneous, well educated and mostly accessible to medial facilities, and health disparities seem far less common compared with the U.S.. Data generated from a trial to further improve in gestational age and birth weight outcomes in Japan would be very helpful to the other industrialized countries. What are the contributing factors to the rising premature rate in Japan? Assisted reproductive technology (ART) is advanced in Japan and contributes to the increase in multiple pregnancies and thus premature and LBW births to some extent. However assuming the rate of ART involved birth at 0.1% in Japan, even with the disproportionately high premature and LBW rates, the rising rates cannot be explained by ART alone. Among the risk factors associated with 'idiopathic premature deliveries', smoking and psychosocial stress might be reasonable target areas for an intervention in Japan because of the size of the population involved and proven causality. The population attributable risk of maternal smoking to LBW was 7.4% in 2000 in Japan.[4] The statistics by the same group at the National Institute of Public Health in Japan indicates that

the smoking rate among pregnant women in Japan is approximately 30% for teenage women and 21% at 24 years old.[25] These figures are likely underestimated because secondary exposure from smoking partners' was not included. The prevalence of women with stressful lives may be even higher. That stressful life soon after conception is associated with a higher miscarriage rate.[26] This particular study implies that this outcome may have been already determined by the time pregnancy is diagnosed. Indeed, to address smoking and psychosocial stress, epidemiological data are needed such as co-morbidities and lifestyles by interviewing and examining women during preadolescent and adolescent periods, pre-pregnancy and inter-pregnancy periods in addition to a gestational period. Taking such a step is a huge task and of complex design and requires exorbitant resources. Maternal fetal medicine and neonatology made a progress and will continue to improve the birth outcomes of prematurity. However, to have a significantly larger impact on the reproductive outcomes at the national level in Japan, USA or any other industrialized country, there needs to be a proactive strategy. Accurate data can lead to effective intervention programs. It will require cooperation among obstetricians, pediatricians, and professionals from disciplines such as public health, social science, social work, nursing, policy making, and industry. The group would have to work cohesively and consistently for data collection, implementation and maintenance of programs.

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