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Chapter 1

Constitutional and Environmental Factors Leading to a High-Risk Pregnancy

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Definition of a High-Risk Pregnancy

Each pregnancy is a unique, physiologically normal episode in a woman's life. However, preexisting disease or unexpected illness of the mother and/or the fetus may complicate the pregnancy.

Risk is defined as the probability that an adverse condition or event will occur within a stated period of time by exposure to specified health hazards (e.g., smoking) or by the presence of one or more ascertainable characteristics (risk factors, or indicators) (e.g., ethnicity, advanced maternal age).

A pregnancy is defined as *high risk* when the probability of an adverse outcome for the mother or child among the "exposed" population is increased over and above the baseline risk of that outcome among the reference ("unexposed" or general) pregnant population. This classification does not take into consideration the magnitude of risk or the importance of the risk to the health outcome of the pregnant population at large (attributable risk).

Mathematical Concepts of Risk

In scientific research risks are commonly expressed as:

- *Relative risk (RR)*, which is synonymous with *risk ratio*, i.e., the ratio of the risk of adverse outcome among the "exposed" population to the risk among the "unexposed" population,

or:

- *Odds ratio (OR)*, which is synonymous with the relative odds, i.e., the ratio of two odds in a population. The OR approximates to the RR if the disease is relatively rare.

If the RR (or OR) is greater than 1 and the 95% confidence interval (CI) does not cross 1, then "exposure" is typically considered to be statistically significantly associated with adverse outcome.

RR (and OR) values indicate the actual probability of an adverse event occurring among the "exposed" population. This actual risk is often referred to as absolute risk. It can be calculated from the frequency of occurrence of the adverse condition among the reference population (prevalence, expressed as probability or odds) multiplied by the given value of the RR (or OR).

A third way to quantify associations is the absolute risk reduction (ARR), which is the difference between the probability of an adverse outcome in the "exposed" population and in the "unexposed" population.

In order to assess the effectiveness of a healthcare intervention, such as medical treatment, one could calculate the number needed to treat (NNT), which refers to the number of patients that need to be treated in order to avert one bad outcome. In other words, how many people do you need to treat in order to benefit one person? The NNT is the inverse of the ARR (NNT = 1/ARR).

Constitutional Risks

Ethnicity and Race

Ethnicity and race are complex, controversial sociologic issues that are difficult to measure accurately. Race and ethnicity are often considered surrogate measures for standard of living and lifestyle. However, both between and within ethnic populations, marked variations occur in cultural beliefs and practices, language, household structure, sexual behavior, contraceptive patterns, general health,

perception of illness and disease, childbirth and child-rearing practices, postnatal customs, dietary habits, housing, education, employment, economic status, level of assimilation, stress, and access to healthcare services. Some of these attributes have little to do with health or disease, whereas others may be important factors. In clinical research, the terms *race* and *ethnicity* are often defined inadequately, if at all. Therefore, reported epidemiologic associations with health problems should be interpreted cautiously.

Risks

Black race is one of the factors that is most strongly associated with low birth weight.[1–5] Low birth weight is closely related to perinatal mortality and may affect both short- and long-term health (fetal programming: the intrauterine origin of adult disease).[6] In the United States, preterm birth rather than growth restriction is implicated as the most important cause of low birth weight in infants born to black women. Given the high rates of preterm delivery, crude survival rates for black infants are less favorable than those for white infants.[5,7,8] The biologic explanation for the high preterm delivery rate among black women is unclear. The excess birth-weight-specific mortality in black infants may be compounded by a failure to seek or receive optimal medical care.[9]

Many preexisting diseases and problems that may influence pregnancy, or occur during pregnancy, have both ethnic and geographic distributions. These diseases, problems, and pregnancy complications in relation to ethnicity are summarized in Table 1.1. Uterine fibroids occur more often in black women than in white women.[10] Nonengagement of the fetal head late in pregnancy is not uncommon in black primigravidae.[11] The available data on ethnic differences in the frequency of dysfunctional labor are inconclusive.

Management Options

Information, screening, and appropriate counseling services should be made available for communities that are considered at risk for specific diseases or pregnancy complications (see Table 1.1 and other relevant chapters).

Prenatal

Communication is often a problem because of language barriers. Video displays and informative pamphlets or brochures written in several languages should be made available.[12] Standard information should include guidelines for lifestyle and nutrition as well as preparation for parturition and parenthood, preferably in keeping with sociocultural features of the relevant ethnic communities. The use of interpreters, either in person or by telephone, is advisable for dealing with specific problems.[12]

Once prenatal care has been initiated, women at risk for specific diseases, such as hemoglobinopathies or infectious diseases, may be selected for further testing or treatment.[13] In parous women, it is important to obtain all necessary information about the course and outcome of previous pregnancies. Immunization status should be checked, and fetal growth should be monitored. Prenatal counseling for inherited diseases should be discussed and offered if appropriate. A delivery plan including the intended mode of delivery should be discussed during the last weeks of pregnancy.

Labor and Delivery

The continuous presence of a supportive female companion (doula) during labor and delivery benefits maternal wellbeing by improving satisfaction, shortening labor, decreasing the need for intrapartum analgesia, and lowering the incidence of operative delivery, including cesarean section and instrumental vaginal birth.[14] Continuous support was most effective when the provider was part of neither the hospital staff nor the woman's social network.[14] It is unlikely that ethnicity in itself affects the duration of labor and delivery. Some studies show a small increased rate of cesarean section in African-American black women.[15]

Postnatal

Exclusive breastfeeding for at least 6 months should be encouraged, an advice that in fact is valid for all women, in both developing and developed countries.[16] Contraceptive advice should take into account individual sociocultural norms and values.[17,18]

Table 1.1 Risks in pregnancy associated with race and ethnicity

Ethnic group	Risks	Screening, counseling, intervention
Middle East Whites, South-East Asians, Indian Asians	Beta-thalassemias (OMIM 613985) are characterized by reduced production of hemoglobin A (see Chapter 35). Minor: clinically heterogenous; anemia in pregnancy. Major (Cooley anemia): rare to survive to reproductive age, but those who do often have pelvic bony deformities and problems with labor and delivery; also iron overload resulting from regular red cell transfusions with subsequent hepatic, endocrinologic, and myocardial damage.	Screening: full blood count (EDTA-anticoagulated blood). Further investigation, such as alkaline electrophoresis or other methods such as iso-electric focusing (IEF) and high-performance liquid chromatography (HPLC) is indicated when mean corpuscular volume (MCH) is < 27 pg. Counseling: carriers of beta-thalassemia are diagnosed by reduced MCH level and raised A_2 levels. Partner testing in women who are carrier of beta-thalassemia. Intervention: if the fetus is at risk of inheriting beta-thalassemia, invasive testing (trophoblast biopsy together with restriction endonuclease analysis of fetal DNA) may be offered.
	Alpha-thalassemias (OMIM 604131) are characterized by one or more dysfunctional genes that are involved in the production of the alpha polypeptide hemoglobin chains (see Chapter 35). Minor: four different genotypes; the more alpha genes affected, the more significant the thalassemia and clinical symptoms. Hemoglobin H disease (three abnormal genes): in adults, usually manifests as a hemolytic anemia of variable severity. Major (Bart's fetal hydrops) (four abnormal genes): nonviable. This condition is associated with severe preeclampsia in the mother.	Screening: MCH and HbA_2 levels are not informative. Counseling: definitive diagnosis can only be made by DNA testing. Partner testing is indicated in women who are carriers of alpha-thalassemia. Intervention: if the fetus is at risk of inheriting alpha-thalassemia, invasive testing (trophoblast biopsy for fetal DNA) should be offered.
Blacks, Mediterranean and Middle East Whites, Indian Asians	Sickling disorders (especially hemoglobin SS or SC [HbSS, HbSC]) (OMIM 603903) (see Chapter 35). Maternal (compound heterozygous or homozygous sickle cell disease): infection, vaso-occlusive sickling crises, acute chest syndrome, renal compromise, jaundice. HbAS (carrier state) mothers are not at risk for sickling crises. Fetus: possible risk of inheriting the disease; fetal growth restriction is a risk with HbSS and HbSC.	Screening: rapid "sickle screening test," IEF, or HPLC. Counseling: prenatal counseling is required. Subsequent testing of the partner is indicated if the woman is heterozygous, compound heterozygous, or homozygous. Intervention: offer invasive prenatal diagnosis if the fetus is at risk of sickle cell disease. The affected fetus is usually not anemic, due to the high circulating levels of fetal hemoglobin (HbF).
Mediterranean Whites, African-American	Glucose-6-phosphate dehydrogenase (G6PD) deficiency (OMIM 305900) is an X-linked hereditary genetic defect. Most female carriers	Screening: population screening is indicated in areas with relatively high prevalence of G6PD deficiency ($> 3\%$) in

Table 1.1 (*cont.*)

Ethnic group	Risks	Screening, counseling, intervention
Blacks, sub-Saharan Blacks	are asymptomatic. Several drugs, including antimalarials, sulfonamides and nitrofurantoin, may trigger acute hemolysis in subjects with G6PD deficiency. Fetus: risk of inheriting the disease including fetal hydrops and severe neonatal hyperbilirubinemia, which may lead to neurodevelopmental disorders.	males. There are two rapid diagnostic tests: a fluorescence spot test and a formazan-based spot test. The gold standard for measuring G6PD activity is the quantitative spectrophotometric assay. Counseling: there is a considerable genetic heterogeneity among affected individuals, the majority of G6PD variants not being associated with any significant morbidity. Intervention: phototherapy is the mainstay of treatment of newborns with hyperbilirubinemia, with exchange transfusion for those who do not respond to phototherapy.
Asians, Chinese, African Blacks	Hepatitis B (chronic carriers): risk of transmission to the fetus or neonate, and to healthcare workers.	Screening: hepatitis B surface antigen (HBsAg) is the universal serologic test for the detection of hepatitis B virus infection. Counseling: a positive HBsAg test indicates acute or chronic hepatitis B. Further blood tests to evaluate the stage of hepatitis B virus infection. Sexual partner and household contacts should be tested and vaccinated, where indicated. Intervention: a fetal scalp electrode should be avoided. Most countries recommend newborns of HBsAg-positive mothers to receive hepatitis B immunoglobin and the first dose of vaccine within 12 hours after birth. Follow-up vaccinations are given for long-term protection. (See Chapter 24)
African and Caribbean Blacks	HIV infection: risk to the mother of symptomatic infection; risk to the fetus and healthcare workers of acquiring the infection.	Screening: three screening assays for the identification of HIV infection: enzyme-linked immunosorbet assay (ELISA), the rapid latex agglutination assay, the dot-blot immunobinding assay. A positive test should be confirmed. Counseling: women should be counseled about the risks of the condition for themselves and the fetus/newborn. Intervention: antiviral therapy should be started before delivery to reduce transmission of the infection to the fetus. (See Chapter 25).
African Blacks	Malaria is a protozoan disease caused by any one of four plasmodium species: *P. vivax, P. ovale, P malariae*, or *P. falciparum*. Malaria in pregnancy is associated with severe infection,	Screening: there is no universal screening test available. When the patient is developing fever and malaria is suspected, prompt diagnostic testing is required.

Table 1.1 (*cont.*)

Ethnic group	Risks	Screening, counseling, intervention
	anemia. Fetus: fetal growth restriction.	The diagnosis is based on both thin and thick blood smears to identify the species of infecting parasite. Counseling: congenital malaria is relatively rare due to the low transmission rate of plasmodium species. However, counsel women about the more likely risks of severe infection, anemia, and fetal growth restriction. Intervention: oral antimalarial treatment. (See Chapter 28).
African (especially Horn of Africa) Blacks	Female genital mutilation (FGM) including clitoridectomy,"excision" which involves the removal of the clitoris and part or all of the labia minora, and "infibulation" which involves the removal of the clitoris, all of the labia minora together with part or all of the labia majora, and the stitching of the two sides of the vulva, thereby leaving a narrow opening for the urinary and menstrual outflow. Depending on the severity of the FGM, problems with vaginal delivery (dystocia, trauma, hemorrhage) are expected.	Screening: delicate inquiry into a history of traditional FGM and potential subsequent medical complications. Counseling: careful handling of requests for operative reversal following vaginal delivery. Intervention: surgical restoration of the "normal" anatomy during or after pregnancy, where indicated. (See Chapter 3).
African Blacks	Uterine fibroids: risk of delivery problems and postpartum bleeding.	Screening: universal screening is not warranted. Counseling: there is a considerable variation in clinical signs and symptoms among affected individuals, most being asymptomatic. The risk of postpartum hemorrhage is increased. Intervention: not specific. (See Chapter 53).
African Blacks, African-American Blacks	Preeclampsia: risks to the mother, including convulsions, cerebrovascular accidents, HELLP syndrome. Risk to the fetus of death or severe morbidity resulting from fetal growth restriction, fetal asphyxia, and/or preterm birth.	Screening: blood pressure measurement is the core of the assessment of maternal health. Counseling: normotensive women with high blood pressure during the second half of pregnancy should be further assessed for signs and symptoms of preeclampsia. Intervention: close maternal surveillance of blood pressure and fetal condition, where indicated, and timely delivery, thereby balancing maternal and fetal risks. (See Chapter 32).

Table 1.1 (*cont.*)

Ethnic group	Risks	Screening, counseling, intervention
Indian Asians	Gestational diabetes: risk to the fetus of death or severe morbidity, in particular fetal intrapartum trauma resulting from macrosomia.	Screening: the screening tests for gestational diabetes are set against imperfect reference standards, such as the oral glucose tolerance test (OGTT), with conflicting diagnostic thresholds. In fact, no universally agreed screening policy for the identification of gestational diabetes exists. Counseling: the efficiency of screening for gestational diabetes may be improved by restricting screening to women at increased risk (targeted screening), such as overweight and obese women. Intervention: diet and insulin, where indicated. (See Chapter 40).
African Blacks, Asians	Preterm delivery: risk to the fetus of death or severe morbidity.	Screening: screening for risk factors for preterm labor by means other than historic risk factors is not beneficial in asymptomatic women. In fact, no universally agreed screening test for identifying women at risk of preterm labor exists. Intervention: there is no universally agreed successful intervention strategy. (See Chapters 23 and 56).
Mexican Whites, Asians, Chinese	Molar pregnancy (hydatidiform mole): increased risk of hyperemesis gravidarum and preeclampsia/eclampsia before 24 weeks of gestation. Risk to the mother to develop choriocarcinoma, in particular among women with complete mole.	Rare abnormality (approximately 1 in 1000 pregnancies) diagnosed by characteristic appearance on ultrasound and gestational-age-specific serum hCG levels higher than expected. Counseling: complete mole is normally associated with normal karyotype, while partial mole is mostly triploid (69, XXX, 69, XXY, or 69, XYY). Intervention: evacuation by vacuum aspiration and follow-up monitoring for persistent trophoblast proliferation/ malignancy. (See Chapter 5).
White Ashkenazi Jews	Autosomal recessive genetic diseases such as Tay–Sachs disease (TSD) (OMIM entry 272800). TSD is an autosomal recessive, progressive neurodegenerative disorder which, in the classic infantile form, is usually fatal by age 2 or 3 years. It is caused by mutations in the hexosaminidase A (HEXA) gene.	Screening: DNA testing is the most cost-effective and efficient approach to carrier screening for TSD in individuals of confirmed Ashkenazi Jewish ancestry. (See Chapter 4).

Summary of Management Options

Pregnancy in women from different ethnic and racial backgrounds

Management options – general	References
Prepregnancy	
The integration of preconception care services within a larger continuum of women's health care should be promoted	19
Provide education, screening, and counseling for communities at specific risk	13
Prenatal	
Overcome language and cultural barriers	12
Offer screening and counseling where specific risk exists	13
Offer prenatal diagnosis if appropriate	13
Provide maternal and fetal surveillance for any specific risk	1,3–5
Labor and delivery	
Offer the continuous presence of a supportive companion during labor and delivery.	14
Postnatal	
Encourage breastfeeding	16
Offer contraceptive advice, taking account of individual sociocultural norms and values	17,18
Management options – specific	
Growth restriction – see Chapter 28	
Preterm labor and delivery – see Chapters 23 and 56	
Preeclampsia – see Chapter 32	
Diabetes – see Chapter 40	
Hemoglobinopathies – see Chapter 35	
G6PD deficiency – see Chapter 35	
Hepatitis – see Chapter 24	
HIV – see Chapter 25	
Malaria – see Chapter 28	
Fibroids – see Chapter 53	
Female genital mutilation – see Chapter 3	
Molar pregnancy – see Chapter 5	
Inherited conditions – see Chapter 4	

Socioeconomic Status

The effect of maternal social factors on the health and wellbeing of the offspring is well known. However, caution should be exercised in interpreting studies of the effect of social conditions on pregnancy outcome, because of variations in definitions and practices in time and geographic area, availability of reliable data, the presence of confounders, and interpretation of the findings. However, the most important variation may be due to confounding factors such as obesity, smoking, and other intoxications.[20–22]

Table 1.2 Social class by occupation of the father

Category	Occupation
I	Higher professionals
II	Other professionals, including those in managerial and technical positions
IIIa	Skilled workers, nonmanual
IIIb	Skilled workers, manual
IV	Partly skilled workers
V	Unskilled workers

From http://www.bsa.natcen.ac.uk/latest-report/british-social-attitudes-31/technical-details/questionnaire-versions.aspx.

Various measures of social status are used, some of which tend to be crude and meaningless. In England and Wales, for example, the maternal social class index is traditionally derived from the Registrar General's Classification, which is based on the occupation of the father of the child (Table 1.2). Other criteria of categorization include educational attainment, income, type of health care, employment, legitimacy, family affluence, household characteristics, and ethnic background.[1,22] Although there is a strong association between social class, however defined, and infant mortality, this observation does not explain why some infants die and others do not in a given social class.

Social adversity probably represents a wide range of behavioral, environmental, medical, and psychological factors that are causally related to pregnancy outcome, some of which are more amenable to intervention than others. In scientific research, correlations with socioeconomic status should be the impetus for further investigation, rather than the endpoint of an analysis.[23]

Risks

Lower socioeconomic status is associated with an increased risk of various adverse pregnancy outcomes, including perinatal mortality, preterm birth, and low birth weight.

Factors that impact further on this risk include:

- Smoking has been suggested as the key factor underlying socioeconomic differences in the prevalence of low birth weight and infant mortality.[5,22,24–27]
- Differences in medical care received by different social classes may also account for some of the extra risks.
- The contribution of poor nutrition is discussed below.

Management Options

Prenatal

If the opportunity arises to provide prepregnancy advice to women of lower socioeconomic background, it should be directed at cessation of smoking and family planning.

Socially disadvantaged women are less likely to seek prenatal care, and also have more pregnancy complications such as fetal growth restriction (FGR). Some claim that apart from recognizing the increased risk associated with socioeconomic disadvantage, there is little to do in terms of intervention. Social support, however, benefits women psychologically, although the effect of social intervention on mean birth weight, low birth weight, and preterm delivery is limited.[15,28]

Labor and Delivery

Intrapartum management need not be substantially modified if no other risk factors are present.

Postnatal

Women of higher socioeconomic status tend to breastfeed more often and longer than women of lower socioeconomic status. Thus, breastfeeding for 6 months should be encouraged for all and social and other support provided, when indicated.[16] Contraception must be discussed.[18]

Summary of Management Options

Pregnancy in women of low socioeconomic background

Management options	References
Prepregnancy	
Recommend health education measures specifically Directed at smoking cessation and family planning	27
Prenatal	
Encourage patients to seek preconception care	19,29,30

(*cont.*)

Management options	References
Provide specific and directed social support	15
Look for clinical evidence of poor fetal growth	24
Labor and delivery	
No additional measures are needed on the basis of adverse socioeconomic factors alone	
Postnatal	
Encourage breastfeeding	16
Provide specific and directed social support	15,28
Discuss contraception	17,18

Parity/Gravidity

Definitions

Gravidity refers to the total number of times the woman has been pregnant, irrespective of the duration, location, number of fetuses, and pregnancy outcome. Hence, gravidity includes (early) miscarriages and ectopic pregnancies. A primigravida ("gravida 1") is a woman who is pregnant for the first time.

Parity, however, refers to the number of times a woman has given birth to a potentially viable infant, dead or alive, in a pregnancy lasting more than 20 weeks. The formal gestational threshold for viability varies between countries (e.g., 20–28 completed weeks of gestation). Parity is irrespective of the number of children of the index pregnancy (e.g., singletons or twins). A nullipara ("para 0") is a woman who has never given birth to a child. Women who have given birth to five or more children are grand multiparous women, while giving birth to ten or more is called great grand multiparity.

Pregnancy losses under 20 weeks of gestation are considered to be miscarriages or (late) abortions, which may be spontaneous or induced.

Incidence

In western societies, nulliparous women constitute approximately half of all pregnant women. Grand multiparity still constitutes a considerable percentage of all deliveries: in 2013 in the United States this percentage was 4.9%.[2]

Risks

Parity is closely correlated with maternal age, and to a certain extent also with socioeconomic status. On the whole, the risk of adverse outcome with parity does not show a consistent pattern. Mean birth weight for infants born to nulliparous women is consistently lower than that for infants born to multiparous women, and this accounts for most of the differences in mortality risk in the offspring of nulliparous and multiparous women.[31] Differences in the mean birth weight of infants born to women of different parity are partially explained by differences in maternal weight. Nulliparity is associated with an increased risk of pregnancy-induced hypertension, which in turn is strongly related to low birth weight. Further, in nulliparous women, there is an increased risk of perineal trauma as a result of either episiotomy or spontaneous perineal rupture.

Women of high parity tend to receive inadequate obstetric care, owing to delays in seeking care and poor attendance. Moreover, it is assumed that women with a history of rapid or precipitated childbirth have an increased risk of unattended out-of-hospital delivery. Grand multiparity is associated with an increased likelihood of abnormal placentation, macrosomia, abnormal fetal presentation, and obstetric hemorrhage.[32,33] On the other hand, labor augmentation and soft tissue lacerations show a lower incidence. Parity, however, does not have a significant effect on the incidence of Down syndrome when the effect of maternal age is taken into account.[34]

Management Options

Prenatal

Nulliparity is a nonspecific risk factor and no specific precautions need to be taken.

In parous women, it is of fundamental importance to obtain all clinically relevant details of previous

pregnancies, which will guide patient-specific care. Provision of childcare facilities may facilitate prenatal care.

Labor and Delivery

There is a difference in the normal labor patterns of nulliparous and multiparous women. A large US multicenter retrospective study among 62,415 parturients with a singleton term gestation, spontaneous onset of labor, vertex presentation, vaginal delivery, and normal perinatal outcome demonstrated that nulliparous and multiparous women appeared to progress at a similar pace before 6 cm. However, after 6 cm, labor accelerated much faster in multiparous than in nulliparous women.[35] In fact, if the maternal and fetal conditions are satisfactory and progress is occurring, with descent of the presenting part, obstetric intervention is not warranted. Cephalopelvic disproportion, however, must be considered when progress in labor is slow. For women with a history of rapid or precipitated delivery, timely admission to the hospital and elective induction of labor are often considered, although there is no evidence that this approach is beneficial.

Postnatal

Discussion of long-term contraception is recommended for all women.[17,36]

Summary of Management Options

Pregnancy and parity

Management options	References
Prepregnancy	
Discuss the risks, with emphasis on the effects of parity alone and nulliparity or grand multiparity (≥ 5)	33,34
Prenatal	
Encourage regular attendance for care in those of high parity	33
Look for pregnancy-induced hypertension in those of nulliparity	33
Look for abnormal presentation from 36 weeks' gestation in those of grand multiparity	33
Labor and delivery	
No specific recommendations are needed on the grounds of parity alone	33
Postpartum hemorrhage is more likely with increasing parity	33
Postnatal	
Discuss long-term contraception	17,36

Age

Adolescent Pregnancy

Definitions

Epidemiologically, a distinction is often made between pregnancy rates among adolescents aged 15–19 years and those among adolescents aged 10–14 years.[37–39] *Reproductive age* is the interval from the age of menarche to the chronologic age at conception, whereas *gynecologic age* is the time span from the age of menarche to the chronologic age at delivery. With the improvement of socioeconomic conditions, the median age of menarche has shown a downward trend. The median age of menarche in developed countries is currently 12.5 years. Conception or delivery within 2 years after the onset of menarche represents the lower extreme of the distribution of both reproductive and gynecologic ages.

Incidence

Teenage birth rates vary more than 10-fold from one country to another.[37] However, birth rate does not reflect pregnancy rate, since the first is influenced by (1) the rate of pregnancy termination, which is relatively high among women aged 15–19 compared to women in other age groups, and (2) the rate of spontaneous miscarriage, which is not influenced by young age.

The UK birth rate among women aged 15–19 was 19.7 per 1000 women in 2012. This birth rate has fallen