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Polycystic Ovarian Syndrome and Fertility

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Abstract: Polycystic ovary syndrome (PCOS) is a common endocrinopathy that has been associated with impaired fertility. This chapter reviews the underlying pathophysiology of PCOS and the associated fertility barriers of the condition. Psychologic concerns, hypothalamic-pituitary, ovarian, and mitochondria dysfunction, obesity, and the role of vitamin D in PCOS are considered with respect to fertility. Lastly, pregnancy risk factors associated with PCOS are also reviewed.
Key words: polycystic ovary syndrome, infertility, anovulation, hyperandrogenism, vitamin D, pregnancy

Introduction

Polycystic ovarian syndrome (PCOS) is the most common female endocrine disorder with a reported prevalence ranging from 4% to 18% among women of reproductive age.[1,2] Several diagnostic criteria have been established for the diagnosis of PCOS which are covered in detail in a previous chapter. PCOS is characterized by chronic anovulation, clinical or biochemical hyperandrogenism, and polycystic ovaries. PCOS is associated with several clinical manifestations including obesity, impaired glucose tolerance, metabolic syndrome, type 2 diabetes mellitus (DM), dyslipidemia, and cardiovascular disease[2]; the severity and presentation of these symptoms may vary widely among the population and within an individual over time. The etiology of PCOS is unknown and unfortunately, there is no cure. Current management is dependent on the treatment of symptoms and mitigation of risk factors for associated conditions.

Infertility or subfertility is a frequent concern among individuals diagnosed with PCOS with a reported prevalence varying widely. Infertility is defined as the failure to achieve a clinical pregnancy after 12 months or more of regular sexual intercourse in women 35 years of age and below or after 6 months or more in women above 35 years

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of age.[3] While infertility affects nearly 12% of couples worldwide, the American Society of Reproductive Medicine (ASRM) estimates the rate of infertility to be between 70% and 80% among individuals with PCOS.[4] Thus, ASRM recommends that an infertility evaluation in women with PCOS begin after 6 months of attempting to conceive without success.[4] According to the Centers for Disease Control (CDC), PCOS is the most common cause of infertility owing primarily to the hallmark symptom of anovulation,[5] however, several other features of PCOS are also thought to contribute to the inability to conceive, namely obesity and insulin resistance. This chapter will provide an overview of the causes of infertility and will address fertility concerns among women with PCOS.

PSYCHOSOCIAL ASPECT OF FERTILITY CONCERNS

Infertility has profound implications for an individual and their communities. Individuals most commonly report distress, depression, anxiety, sexual dysfunction, lower self-esteem, and social discord following an infertility diagnosis. This holds true for individuals diagnosed with PCOS. The uncertainty surrounding fertility is worrisome to adolescents and women diagnosed with PCOS. In one study, girls with PCOS were found to be 3.4 times more likely to be worried about their ability to become pregnant than the control group, and this concern about future fertility was associated with significant reductions in quality of life (QOL).[6] Another study also demonstrated that the potential for infertility has a negative impact on the QOL among adolescent girls diagnosed with PCOS.[7] Holton et al[8] reported that these concerns arise out of perception on the part of the individual with PCOS that it will be difficult for them to conceive, and thus there is a desire for preconception counseling and evidence-based educational materials so that patients can make informed decisions surrounding their reproductive and sexual health.

The uncertainty surrounding fertility can be particularly distressing for individuals with ties to communities with strong values and ideals of fertility. While such data is limited, a study conducted in Vienna, Austria found that Muslim immigrant women diagnosed with PCOS who presented to a University Clinic reported a much stronger desire for childrearing and more distress related to an infertility diagnosis compared with European women with PCOS.[9] Thus, it is important to keep in mind that women with PCOS dealing with infertility from various sociocultural backgrounds may have different psychosocial pressures and needs.

A prospective cohort study from 2016 evaluated the QOL in 2 groups, 1 group consisted of females with PCOS and their partners, while the other group was comprised of women with unexplained infertility and their partners. Using a validated assessment, the fertility-specific QOL survey, women in each cohort were evaluated at baseline before initiation of fertility treatment. Women with PCOS had lower fertility-specific QOL scores (72.3 ± 14.8) than those with unexplained infertility (77.1 ± 12.8; $P < 0.001$); this trend held true for each domain (social, mind/body, emotional) evaluated in the study with the only exception being in the relational domain.[10] The authors suggest the differences in scores seen between the 2 cohorts were largely explained by variation in body mass index (BMI), hirsutism, household income, and age.[10] Furthermore, the women in both groups had lower scores than their male partners. This study underscores that women with PCOS, particularly those with higher BMI, hirsutism, and of lower socioeconomic class, may need closer observation and when appropriate, offered mental health support given the increased emotional and physical distress of the condition.[10]

HYPOTHALAMIC-PITUITARY DYSREGULATION

In PCOS women, there is a unique interplay between the hormones involved in the

hypothalamic-pituitary axis that culminates in chronic anovulation and consequently infertility. Unlike in normal cycling women who undergo hormonal variations throughout the menstrual cycle in response to different hormonal cues, women with PCOS have a relatively constant release of gonadotropins. The invariable luteinizing hormone (LH) pulse frequency in PCOS women mimics the frequencies classically seen in the late follicular phase of normal ovulatory women; a pattern that favors LH over follicle-stimulating hormone release.[11] In PCOS women, LH secreted by the anterior pituitary in response to gonadotropin-releasing hormone (GnRH) is characterized by increased pulse frequency, and to a lesser degree also an increase in pulse amplitude.[12] In addition, the LH receptors in PCOS women have a heightened response to GnRH when compared with non-PCOS women.[13] The abnormal secretory dynamics described above are evident by the elevated serum LH levels and high LH/follicle-stimulating hormone ratio classically seen in PCOS women.

It is postulated that hyperandrogenism, which is a cornerstone of PCOS, may also increase GnRH pulse activity, leading to both greater LH receptor sensitivity and elevated LH secretion.[13] In an effort to see if the androgens impacted LH secretion, Eagleson et al[14] treated women with PCOS and a control group with progesterone either alone or with estrogen (combination oral contraception). Upon administration of the hormone treatment, both groups had a decrease in LH levels, however, it was more pronounced in the control cohort. However, when women with PCOS who were treated with the antiandrogen flutamide, following either progesterone or the combination of oral contraception treatment, the women had restoration of LH levels similar to normal controls.[14] These findings corroborate the notion that elevated androgens inhibit the normal negative feedback of estrogen and progesterone on LH pulse release and play a role in normal hypothalamic-pituitary function.

OVARIAN DYSFUNCTION

The morphologic characteristics of PCOS consist of 2 main features: an increasing number of antral follicles, and increase size and density of the ovarian stroma. While a subset of women with these ovarian features are ovulatory, for many follicular growth ceases once it reaches 5 to 8 mm in diameter. This failure to form a dominant follicle leads to anovulation and subsequent infertility. The dense ovarian stroma is primarily composed of theca cells. The theca cells convert cholesterol to androgens through a succession of intermediary steps, with the primary output being androstenedione followed by progesterone, 17alpha-hydroxyprogesterone, and dehydroepiandrosterone.[15] The androgen overproduction by the theca cells in PCOS ovaries, as well as the hyperresponse to LH provocation by these cells is one of the key reasons for the hyperandrogenic ovarian milieu in PCOS patients.

While androgens serve an important physiological function in follicle development, hyperandrogenism has been shown in numerous animal studies to have an aberrant effect on follicular development leading to negative effects on ovarian function. One study by Bertoldo et al[16] found that isolated preantral and antral follicles from PCOS mice resulted in slower growth compared with controls, and antral and preovulatory PCOS follicles exhibited reduced follicle health compared with controls. This study also found that PCOS female mice showed a poorer response to hyperstimulation and impaired oocyte function. These findings led the authors to conclude that prolonged exposure to androgen excess leads to aberrant follicle development, which is persistent even after removal from that environment.[16] Thus, although the exact mechanism is unclear, ovarian dysregulation is also a contributor to infertility.

INSULIN RESISTANCE AND FERTILITY

PCOS is commonly associated with insulin resistance and hyperinsulinemia; conditions which are thought to contribute to

the pathogenesis of PCOS. In addition, increased serum insulin levels and insulin resistance have been reported to be associated with decreased cycle ovulation, conception, pregnancy, and live birth rates.[17] In a 2012 study of 45 reproductive-aged women with PCOS and 161 control women, Tsai et al[18] amassed dietary intake, glucose metabolism, and sex hormones for each group. Women with PCOS had elevated postprandial glucose levels, fasting insulin, and insulin resistance compared with women without PCOS, demonstrated by marked metabolic profile differences among the PCOS cohort.[18]

Metformin is a biguanide insulin-sensitizing agent that is often administered for PCOS women with clinical signs or biochemical evidence of insulin resistance, with a goal of improving insulin resistance and correcting the underlying hormonal disruption. Metformin has been proven to be particularly effective in reducing insulin resistance and improving ovulatory performance. New insulin-sensitizing agents are being used in women with PCOS to maximize positive effect on insulin while limiting adverse side effects,[19] as metformin is poorly tolerated by some women due to gastrointestinal distress. Metformin also has been shown to increase ovulation when compared with placebo, however, it is less effective than other oral ovulation-induction agents; thus, metformin should not be utilized as a first-line treatment for this indication.[20] The different medications for ovulation induction are discussed in greater detail in the pharmacotherapy chapter.

VITAMIN D DEFICIENCY AND FERTILITY

Vitamin D has traditionally been associated primarily with bone function and calcium and phosphorus homeostasis, however, expression of the vitamin D receptor in the ovaries, uterus, and placenta have suggested a role for vitamin D in reproduction. The vitamin D receptor is expressed in granulosa cells, cumulus oophorus cells, endometrium, fallopian epithelial cells, placenta, and in the pituitary gland.[2] In addition, the placenta, endometrium, and ovary also express 1α-hydroxylase, the enzyme required to synthesize 1,25-dihydroxyvitamin D_3 or calcitriol the active form of vitamin D.[2] In the endometrial stroma cells, calcitriol regulates expression of the *HOXA10* gene, which is important for successful implantation.[21] Upregulation of *HOXA10* in the endometrium is necessary for embryo implantation. Cermik et al[22] demonstrate *HOXA10* expression was repressed by testosterone in women with PCOS. Endometrial biopsies obtained from women with PCOS demonstrated decreased *HOXA10* mRNA expression levels, indicating a role for testosterone as a regulator of *HOXA10* expression. Diminished uterine *HOXA10* expression may also contribute to the diminished reproduction potential of women with PCOS by limiting embryo implantation.[22]

The vitamin D pathway has been suggested to have a regulatory role in PCOS-associated symptoms. Calcitriol has been associated with follicular growth and development,[23] and it has also been shown to increase the expression of the insulin receptor, insulin synthesis and secretion, and insulin sensitivity.[21] The presence of vitamin D receptor polymorphisms have been shown to be associated with the severity of PCOS phenotype; although these findings are controversial and need further investigation.

While lower vitamin D levels have been associated with ovulatory and menstrual irregularities, lower pregnancy success, hirsutism, hyperandrogenism, obesity, and elevated cardiovascular disease risk factor,[24] the prevalence of vitamin D deficiency among individuals with PCOS is also controversial. Two different meta-analyses reported that women with PCOS had substantially lower levels of vitamin D, yet noted that vitamin D deficiency was more common in a patient in PCOS women who are obese compared with nonobese PCOS women.[25,26] Importantly, a meta-analysis by He et al[27] did not show significant

improvement in markers of insulin resistance nor hyperandrogenism with vitamin D supplementation among individuals with PCOS. Thus, the increased risk of vitamin D deficiency among women with PCOS may be related to associated comorbidities, and not necessarily to the pathophysiology of PCOS itself.

FERTILITY AND MITOCHONDRIA FUNCTION

The relationship of cellular dysfunction and PCOS has garnered attention in a recent investigation, with mitochondria thought to play a large role to the underlying etiology. Mitochondria are the functional "powerhouse" of the cell and play a fundamental role in cell energy metabolism and apoptosis, as well as signal transduction for cell proliferation.[28] The role of mitochondrial function disorders in the pathogenesis of PCOS has been demonstrated by Papalou et al.[29] It may account for several characteristics of PCOS, such as androgen excess, insulin resistance, obesity, abnormal follicular development, and inflammation.

While the exact relationship between mitochondrial dysfunction and PCOS is unknown, there are several factors that are thought to contribute to the disruption.[30] Replication errors are more likely to occur in mitochondrial DNA than in nuclear DNA, which leads to greater mutations, deletions, and mitochondrial DNA molecule depletion. In addition, oxidative stress-induced cellular damage is increased in women with PCOS, and although the exact mechanism is unknown, it is thought to lead to insulin resistance and other metabolic abnormalities, the possibility at the level of the mitochondria. This pathway may also be responsible for cellular changes which lead to the development of metabolic syndrome; a condition often seen in PCOS women characterized by hypertension, increased abdominal adiposity, dyslipidemia, and impaired glucose metabolism.[31] Cellular oxidative stress is closely related to inflammation, and the ability to completely distinguish it from inflammation is quite difficult. Oxidative stress is positively correlated with androgen levels and contributes to hyperandrogenism in PCOS patients. Follicular fluid is complex and contains a mixture of protein, sugar, reactive oxygen species, antioxidants, and hormones.[32] Oocytes have a large quantity of mitochondria that play an important regulatory role in oocyte maturation, fertilization, and preimplantation embryo development.[32] The concentration of these substances directly affects oocyte maturity and quality. Imbalances between antioxidant factors and reactive oxygen species in the follicular fluid may have adverse effects on oocyte quality, fertilization, and embryo development. This process is likely through alteration of the equilibrium of the follicular microenvironment and results in abnormal ovulation and infertility in patients with PCOS.[33] Numerous indicators of oxidative stress are abnormal in the blood and follicular fluid of patients with PCOS and may play a role in infertility among these women.

FERTILITY AND OBESITY

In the United States, nearly 50% of reproductive age women are overweight (BMI > 25 kg/m^2) or obese (BMI > 30 kg/m^2).[34] Obesity alone is a risk factor for hypertension, dyslipidemia, DM, sleep apnea, and cardiovascular disease; thus, elevating the rate of all-cause mortality in this population.[35] Women with PCOS, who manifest the overweight or obese phenotype, can suffer not only from these negative health implications but also from infertility. Obesity is commonly associated with ovulatory dysfunction; women with a BMI > 27 kg/m^2 have a relative risk (RR) of anovulatory infertility of 3.1 [95% confidence interval (CI), 2.2-4.4] compared with their lean counterparts.[36,37] Furthermore, obesity is associated with higher doses of medication to induce ovulation as well as a decreased response to clomiphene citrate [increased BMI: odds ratio (OR): 0.92; 95% CI, 0.40-0.89].[38] Moreover, in a systematic review of 27 in vitro fertilization (IVF) studies showed that women with obesity have

a reduced chance of clinical pregnancy and live birth compared with normal-weight women.[39] This was confirmed in a meta-analysis of 33 IVF studies of over 47,000 cycles which concluded that overweight and obese women have a significantly reduced rates of clinical pregnancy (RR: 0.90, $P < 0.0001$) and live birth (RR: 0.84, $P = 0.0002$) compared with women with a BMI of $<25\ kg/m^2$.[40] It is thought that obesity alters oocyte quality, fertilization, and possibly modifies endometrial receptivity. Hence, weight loss and lifestyle modifications should be highly encouraged in PCOS women who are obese or overweight. These modifications can serve to improved maternal overall health but also can be instrumental in the goal to conceive and maintain a healthy pregnancy.

INFERTILITY TREATMENT

PCOS is strongly associated with infertility and is one of the most common reasons women seek medical assistance. Treatment options vary for women with PCOS-associated infertility and include oral ovulation-induction agents, controlled ovarian stimulation, and IVF. The goal with ovulation induction is single follicular recruitment in efforts to limit the risk of multiple gestations. Careful monitoring is often indicated for PCOS women undergoing fertility treatment given the high risk of multifollicular recruitment, the potential of multiple gestations, and ovarian hyperstimulation syndrome. Cycle cancellation should be discussed with the patient when the response to treatment is deemed too high. Should ovulation-induction treatments fail, IVF is an option. Although ovarian hyperstimulation is of concern given the high number of follicles seen in PCOS women, IVF protocols with consideration about gonadotropin dosing and the use of GnRH agonists triggers have significantly decreased the risk of ovarian hyperstimulation syndrome. Furthermore, IVF allows for a single embryo transfer which significantly lessens the risk of a twin pregnancy. Thus, a stepwise approach to treatment should be formulated for women with PCOS, with strong consideration on treatment modality based on the risk/benefit stratification. The different infertility treatments are discussed in more detail in other chapters.

PCOS AND PREGNANCY COMPLICATIONS

The heterogeneity of PCOS and the paucity of large randomized studies evaluating pregnancy in PCOS patients limits our understanding of the causal relationships of PCOS and adverse pregnancy outcomes. It is clear that the metabolic sequelae associated with PCOS affect all stages in a women's life; hence, it should be of little surprise that there are also some associated obstetric complications due to these metabolic risks. There are have been several meta-analyses which have investigated the association between PCOS and the risk of pregnancy complications. PCOS patients have consistently been associated with an increased risk of gestational diabetes mellitus (GDM), hypertensive disorders in pregnancy, alterations of birth weight, and early pregnancy loss.[41–43]

GDM

GDM is one of the most common obstetric complications seen in 3% to 9% of pregnancies in the United States.[44] Unfortunately, these numbers continue to rise given the increase in obesity, sedentary lifestyle, advancement in maternal age at conception, and the increased use of fertility medications resulting in multiple gestations. GDM is defined as carbohydrate intolerance that begins or is first recognized during pregnancy.[45] The American College of Obstetricians and Gynecologists have adopted the American Diabetic Association (ADA) and National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) guidance on screening for diabetes and prediabetes taking into account not only previous pregnancy history but also risks factors for type 2 DM.[45] Interestingly,

pregnant women with a BMI $>25\,kg/m^2$ and with PCOS, acanthosis nigricans, or any other condition associated with insulin resistance should be screened early in pregnancy given the high risk for type 2 DM.[45]

While there are similar metabolic risks, it is still unclear if PCOS independently increases the risk of GDM, or if this is related to increased adiposity. Mikola et al[46] found that PCOS independently increased the risk of GDM, but that overweight or obese women with PCOS was the strongest predictor for the development of GDM. Similarly, in a meta-analysis of 15 studies, Boomsma et al[43] found women with PCOS demonstrated a significantly higher change of developing GDM compared with controls (OR: 2.94; 95% CI, 1.70-4.08). Furthermore, a subgroup analysis of 5 higher validity studies from Boomsma et al's[43] meta-analysis further reinforced the increased risk of PCOS women developing GDM (OR: 3.66; 95% CI, 1.20-11.16). In a more recent meta-analysis investigating 29 studies, PCOS in pregnancy was again associated with a significantly increased risk of GDM when compared with non-PCOS women (RR: 2.78; 95% CI, 2.27-3.40).[47] Conversely, a large multicenter case-control study of over 2000 women indicated that the increased risk of GDM in women with PCOS was related to obesity and maternal age rather than the underlying PCOS diagnosis.[48] Similarly, 2 case-control studies evaluating PCOS women with non-PCOS women, who were matched by BMI and age, showed no increase in GDM within the PCOS cohort.[49,50] Since there are different PCOS phenotypes, screening for GDM should be underscored in those women with risk factors and an increased BMI as per the current recommendations.

Hypertensive Disorders in Pregnancy

Hypertensive disorders in pregnancy are estimated to affect 6% to 8% of all pregnancy in the United States and is the second leading cause of maternal mortality.[51] This category encompasses various conditions to include chronic hypertension, gestational hypertension, preeclampsia/eclampsia as well as chronic hypertension with superimposed preeclampsia. The different hypertensive disorders are characterized by the onset of hypertension (either prepregnancy, before 20 wk gestation, or after 20 wk gestation), presence or absence of proteinuria, the occurrence of end-organ dysfunction, or seizures. Given that some of the risk factors for hypertensive disorders are also associated with PCOS, namely diabetes and obesity, the association between the 2 conditions seems plausible.

A pooled meta-analysis of 15 studies showed that women with PCOS demonstrated a significantly higher chance of developing a hypertensive disorder of pregnancy when compared with non-PCOS women (OR: 3.67; 95% CI, 1.98-6.81).[43] Similarly, women with PCOS also demonstrated a significantly higher probability of developing preeclampsia than the control cohort (OR: 3.47; 95% CI, 1.95-6.17).[43] It should be noted that in all studies in which preeclampsia was an endpoint there was reported a lower parity, higher BMI, and more multiple gestations among women with PCOS versus controls. Yu et al[47] in a meta-analysis of 29 studies that evaluated preeclampsia and gestation hypertension between PCOS pregnancies versus pregnancies without PCOS showed a harmful impact for both conditions (preeclampsia: RR: 2.79; 95% CI, 2.29-3.38, gestational hypertension: RR: 2.46; 95% CI, 1.95-3.09) in PCOS women. Given the higher likelihood for hypertensive disorders in pregnancy among women with PCOS, careful attention to blood pressure and symptomatology at each prenatal visit and postpartum should be undertaken.

Alteration in Birth Weight

As previously highlighted, there is an increased risk of both DM and hypertensive disorders in PCOS women. Ironically, women with DM are at increased risks of

macrosomia, whereas those women with hypertensive disorders have an increased chance of small for gestational age (SGA) infants secondary to placental insufficiency. In a pooled meta-analysis of 12 studies, the data revealed a statistically, albeit not clinically, significant lower neonatal birth weight among infants of women with PCOS (mean weight difference: −38.4 g; 95% CI, −62.2 to −14.6).[43] However, when a subgroup analysis of 4 studies in which controls were matched for confounders there was no significant difference in birth weight. Similarly, in a meta-analysis pertaining to the outcomes of macrosomia (11 studies) and SGA infants (10 studies) in women with PCOS compared with controls, the data showed that pregnant PCOS women did not have an increased risk of macrosomia (RR: 1.14; 95% CI, 0.96-2.20) or SGA (RR: 1.45; 95% CI, 0.96-2.20).[47] Thus, an underlying PCOS diagnosis does not appear to play a role in the birth weight of the infant.

Early Pregnancy Loss

Spontaneous abortion in women with PCOS has been reported to be as high as 30% to 40%, which is ~3-fold higher than the reported rates of 10% to 15% for women without PCOS.[52] Similarly, individuals with recurrent miscarriage have been found to have a higher prevalence of polycystic-appearing ovaries on ultrasound (40% to 82%), compared with those unaffected (23%).[53] It should be noted, however, that these studies often use nonstandardized diagnostic criteria and varying imagine modalities to assess the ovarian findings. One possible explanation for the observed increase in the spontaneous abortion rate among women with PCOS is the use of ovulation-induction agents including the use of clomiphene citrate. A significantly higher rate of spontaneous abortion has been reported among pregnancies resulting from the use of clomiphene citrate compared with spontaneous pregnancies in patients who are otherwise experiencing subfertility.[54] However, other studies have opposed this claim or suggested this observation may be dose dependent or based on early pregnancy monitoring/testing in this subgroup.[55]

An increase in early pregnancy loss has also been attributed to the increased prevalence of elevated LH levels, hyperandrogenism, insulin resistance, and obesity. Though elevated LH levels have been associated with an increased risk of miscarriage, this has not been found to be predictive of pregnancy loss.[56] Insulin resistance, however, has been identified as an independent risk factor for miscarriage, particularly when not controlled.[57] One study by Wang et al[58] showed that although women with PCOS were found to have an increase in the prevalence of spontaneous abortion compared with women without PCOS, this effect was decreased to nonsignificant and ultimately nil after controlling for obesity and other confounding factors including the type of treatment received. Thus, the increased rate of miscarriage seen among women with PCOS may be secondary to the increased prevalence of obesity, insulin resistance, and other confounding factors.

Conclusions

Women with PCOS are at increased risk for infertility owing primarily to anovulation. However, given the various hormonal perturbations experienced by women with PCOS, several factors likely play a critical role in fertility as addressed in this chapter. While there is still much to glean about the relationship between PCOS and fertility, it is clear that lifestyle modifications, weight optimization, and when indicated, medication may be beneficial. The goal in treating PCOS women is to optimize their health preconceptionally in efforts to achieve a successful pregnancy while minimizing obstetric complications. Women with PCOS should be encouraged that they can successfully conceive and have a healthy pregnancy.

However, more research is still needed to better understand the relationship between PCOS and fertility so that women with PCOS can be appropriately counsel and aided when they seek medical attention.

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