Severe Neonatal Hyperbilirubinemia and Kernicterus: Are These Still Problems in the Third Millennium?

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Kernicterus is a chronic condition characterized by choreoathetotic cerebral palsy, hearing loss, paralysis of upward gaze and, sometimes, intellectual deficits\cite{1-3}. The term kernicterus, which refers to pathologic staining of the brainstem nuclei (Greek for 'jaundice of the nuclei') was first used by Schmorl\cite{4} and has now entered regular medical usage. Additional terms are sometimes used interchangeably, but in fact, designate different entities. Thus classic 'kernicterus' should typically be used in the context of chronic neurologic disease, while the term 'bilirubin encephalopathy' [acute bilirubin encephalopathy (ABE)] should, in fact, refer to the acute phases of the condition seen in the first days and weeks following the acute hyperbilirubinemic event\cite{5}. The term bilirubin-induced neurologic dysfunction refers to a subtle form of brain injury, also due to the effect of bilirubin toxicity, but comprising less obvious neurodevelopmental disorders or manifestations than seen in classic kernicterus. These may include deafness, disorders of auditory processing and visual motor paralysis\cite{2,6}.

Key Words
Kernicterus · Bilirubin encephalopathy · Bilirubin · Glucose-6-phosphate dehydrogenase deficiency · Late prematurity · ABO blood group heterospecificity · Exchange transfusion · Phototherapy

Abstract
Despite efforts to eliminate permanent and irreversible brain damage due to bilirubin encephalopathy and kernicterus, these conditions continue to accompany us into the third millennium. This phenomenon occurs not only in developing countries with emerging medical systems, but in Westernized countries as well. Comprehensive guidelines to detect newborns with jaundice and treat those in whom hyperbilirubinemia has already developed have been formulated in several countries, but have not been successful in completely eliminating the problem. In this appraisal of the situation we review selected aspects of bilirubin encephalopathy and/or kernicterus. We highlight recent reports of severe hyperbilirubinemia and kernicterus, discuss some of the factors responsible for the continuing appearance of these conditions, and briefly review what can be done to decrease bilirubin-related morbidity and mortality to the minimum.

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Much of the clinical material cited in this paper was published after the year 2000, and is thus relevant to current practice. It is not our intention to comprehensively appraise all aspects of kernicterus in this review. Rather, we wish to selectively relate to some aspects of why we continue to see cases of kernicterus, and what we can do to prevent, or minimize, these from occurring.

Did the Pendulum Actually Swing?

Some authors have referred to a disappearance and then resurgence of kernicterus during the last 2 decades [7, 8]. Hansen [3] has likened the situation to a recurrence of an unpleasant situation: ‘the specter walks again’. Undoubtedly, the advent of exchange transfusion, the subsequent introduction of phototherapy and prophylaxis of a major cause of kernicterus, Rh isoimmunization and its associated hemolysis resulted in a decrease in the number of cases of kernicterus in Westernized countries with advanced medical systems. However, there is some controversy as to whether the condition did, in fact, completely disappear for a while and then reappear. Though for a period there were few publications of cases of kernicterus from industrialized countries, one wonders what happened to the cases of kernicterus currently being seen, the result of conditions that have not been eliminated, including glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, direct antiglobulin titer (DAT)-positive ABO isoimmunization and late prematurity. While some cases, especially in the latter group, may have been prevented by longer hospital stays and a more aggressive therapeutic approach, it is difficult to comprehend a disappearance and then reappearance of kernicterus associated with ABO blood group heterospecificity or the sudden, unpredictable and exponential rises in serum bilirubin associated with G-6-PD deficiency [9, 10].

In favor of the resurgence theory, some case reports of kernicterus surfaced in the US after a period of relative ‘publication silence’ [11–13] and culminated in the publication of the provisional (2004) and subsequently final (2009) report of the Kernicterus Registry [14, 15]. In Denmark, in a search of medical registries, insurance and other records, and in direct approaches to each of the pediatric departments in that country, Ebbesen [16] could find no cases of kernicterus during the 20 years preceding 1994, but did uncover 6 cases between 1994 and 1998. Subsequently, during 2000–2001, Ebbesen et al. [17] identified 32 near-term and term infants in whom the serum total bilirubin (STB) values exceeded the indications for exchange transfusion, the median value for which was 450 µmol/l (26.3 mg/dl). Twelve of these infants had signs and symptoms of central nervous system involvement including 11 with evidence of ABE. Many of the infants were readmitted after having been discharged as healthy; readmitted babies frequently had a higher incidence of clinical bilirubin encephalopathy than in those in whom the hyperbilirubinemia developed in hospital. This finding may have been due to higher STB concentrations in combination with prolonged exposure to toxic bilirubin levels. In the US, Burke et al. [18] used data from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample and Kids’ Inpatient databases to determine kernicterus time trends. They reported a 70% decrease in hospitalizations between 1988 and 2005 of neonates with a diagnosis of kernicterus.

On the other hand, Brooks et al. [19], using strict ICD-9 codes for kernicterus from the California Department of Developmental Services, identified 25 cases of physician-confirmed strictly diagnosed kernicterus during the 10-year period of 1988–1997, equivalent to an incidence of 0.44 per 100,000 live births in California during this period. The incidence was constant during the study period and was not significantly different between the periods 1988–1993 and 1994–1997. The same authors studied the issue on a national US basis by extracting mortality data due to kernicterus from the Centers for Disease Control and Prevention databases. Thirty-one infant deaths with kernicterus as an underlying cause were reported from 1979 to 2006. The kernicterus death incidence during the first 14 years of the study period was not significantly different from that of the second study time epoch.

Whether there was or was not a disappearance and resurgence of kernicterus is still not clear. What is important is that, in the year 2011, kernicterus is still with us and making a major contribution to neonatal and childhood mortality and morbidity, as will be seen in the following sections.

Kernicterus in the Third Millennium

Developing Countries

While undoubtedly a tragedy, it is not surprising that kernicterus continues to occur in developing countries, with as yet underdeveloped health services, or in war zones. Perhaps the most devastating of recent reports emanates from Baghdad, Iraq, where there has been a severe breakdown of medical services [20]. Of 162 infants ad-
mitted for severe hyperbilirubinemia [STB up to 770 μmol/l (45 mg/dl)], 22% had advanced ABE, 12% died within 48 h of admission and 21% had posticteric sequelae. Almost all babies were <10 days old. Evidence of advanced ABE at the time of admission increased the risk for the adverse outcome of kernicterus or death eightfold. Some other reports from developing countries since the year 2000 derive from Nigeria [115 babies with ABE, of whom 42 (36.5%) died] [21], Oman [14 cases of whom 4 (28.5%) died] [22] and Turkey [10 G-6-PD-deficient neonates, of whom 5 (50%) developed kernicterus] [23]. In Kuwait and the United Arab Emirates, newborns with kernicterus were reported following henna applications to their skin [24].

Westernized Countries

Recent comprehensive reports from Westernized countries emanate from the US [15], Canada [25], the UK and Ireland [26], and Denmark [27]. The US-based Kernicterus Registry provides a record of 125 infants who actually developed kernicterus. The Canadian, UK and Ireland, and Danish studies also included infants with extreme hyperbilirubinemia but without ABE and, in the case of the Canadian survey, infants who had undergone exchange transfusion. The latter 3 surveys were all performed subsequent to the year 2000. Abnormal neurological signs attributable to bilirubin toxicity were seen in 20, 13 and 39% of the Canadian, UK and Ireland, and Danish groups, respectively. Overall, the most common etiologic entities found were ABO blood group heterospecificity (not necessarily DAT-positive) and G-6-PD deficiency, both overrepresented relative to their frequency in the respective background population groups. A striking feature is the readmission of many infants who had been discharged as healthy from birth hospitalization. Breastfeeding played a prominent role in those Danish infants in whom no other etiological cause for hyperbilirubinemia could be found. Black ethnicity and minority groups were also overrepresented, relative to the home population, in the US and UK/Ireland groups.

In a survey of 109 level III neonatal units in Italy, 16 cases of kernicterus were reported during the decade preceding 2010 [28]. Eleven of these cases were in term infants, while 5 were found in preterms. Similarly, between 2003 and 2005, a national surveillance system in Germany uncovered 11 cases of kernicterus [29]. Among this group, late prematurity and readmission of previously healthy babies were common.

Clinical Picture of Kernicterus

Acute Bilirubin Encephalopathy

Newborns with ABE present a clinical picture very different from the chronic form, as recently reviewed [2]. The features associated with severe hyperbilirubinemia include, in the early stages, lethargy and poor feeding. These signs are nonspecific for bilirubin encephalopathy and if not suspected by the treating physician, may lead to delay in diagnosis and timely institution of therapy. As the disease process progresses, muscle tone may fluctuate between hypo- and hypertonia and a high-pitched cry develops. Later, spasm of the extensor muscles with back arching, opisthotonus, retrocollis and impairment of upward gaze resulting in the 'setting sun sign' appear, while fever, seizures, apnea and death may complete the picture [2]. Sgro et al. [30] recently documented the clinical picture of 32 newborns whose STB ranged from 426–773 μmol/l (24.9–45.2 mg/dl) and who had neurological findings at the time of admission. Cardinal clinical features included hypotonia, poor suck, lethargy and abnormal auditory-evoked responses. Opisthotonus, retrocollis, apnea, seizures, irritability and hypertonia were found, but to a lesser extent. Not surprisingly, infants in the highest peak bilirubin level group (>550 μmol/l (32 mg/dl)) who presented within the first 2 days of life or who had exchange transfusion were at higher risk for presenting with signs of bilirubin encephalopathy. The authors suggest that the rapid increase in serum bilirubin in those with early presentation may have potentiated an increased risk of ABE.

Chronic Kernicterus

The clinical picture of kernicterus in its chronic form has been well described [2]. Affected individuals may display a dystonic or athetoid movement disorder, an auditory processing disturbance which may be associated with hearing loss, motor ocular impairment of upward gaze, enamel dysplasia of the teeth, and hypotonia and ataxia due to cerebellar involvement. The 25 above-mentioned California cases of strict definition kernicterus serve to provide a glum picture of these severely disadvantaged children [19]. Seventy-two percent were male. At a mean (SD) age of 7.8 (3.9) years, 60% did not walk at all, and only 16% were able to walk unaided. A feeding tube was in place in 12%, while only 52% could self-feed orally. Severe or profound mental retardation, or severe disablement precluding testing or completion of testing was found in 36%, while only 32% had no evidence of mental retardation. Epilepsy was found in 20%. Severe,
profund or untestable visual impairment was documented in a quarter of the cases. Severe, profound or untestable hearing impairment was a feature affecting 56% of the group, with only 36% having normal hearing. Motor spasticity was seen in 32%, ataxia and dyskinesia in 12% each, and hypotonia in 8%.

Does ABE Necessarily Predict Chronic Disease?

There is some evidence to suggest that the occurrence of ABE may not necessarily translate into permanent neurological sequelae. Harris et al. [31] identified 6 exclusively or partially breastfeeding term and near-term infants from 1993 to 1996 who were readmitted to hospital within the first week of life. Five infants had bilirubin values >513 μmol/l (30 mg/dl) and abnormal neurologic signs were already present at the time of admission in 5 infants. Three of the 4 infants who had initial MRIs had increased signal intensity in the basal ganglia consistent with kernicterus, while 2 had abnormal auditory-evoked responses. Infants were treated aggressively with phototherapy, intravenous fluids and, in 5 of the 6, exchange transfusions. At follow-up examinations between 3 months and 2 years, the clinical signs had resolved in all but 1 infant. Four infants had a subsequently normal MRI and only 1 had residual hearing impairment.

Hansen et al. [32] recently reported 6 infants from 4 European countries who presented with symptoms and signs commensurate with intermediate-to-advanced acute phase bilirubin encephalopathy. Clinical features included seizures, shrill cry, pronounced muscular hypotonia, apnea, anorexia and opisthotonos/retrocollis. In 2 of the 4 infants who had had an MRI performed, findings typical of kernicterus were found. Subsequently, complete normalization was observed in 4 of the 6 infants. The 5th had hearing loss while the 6th had severe residual neurological sequelae.

Similarly, 3 of 11 surviving newborns with bilirubin encephalopathy in the UK and Ireland survey were found to be normal on follow-up [26].

The virtual absence of long-term neurological deficits attributable to bilirubin disease, except for 1 infant, in the above-mentioned Danish infants who were available for follow-up is also noteworthy [27]. However, it must be recognized that only 28% of those originally included were available for these follow-up studies.

STB versus Serum Unbound Bilirubin in the Prediction of Kernicterus

The correlation between increasing STB concentrations and the development of kernicterus in Rh immunized babies with severe hemolysis was described many years ago [33]. More recently, in the post-Rh immunization era, it has become clear that the serum total bilirubin value correlates poorly with the subsequent development of kernicterus. There is also no single cutoff point above which an infant will categorically develop bilirubin encephalopathy and/or kernicterus, or below which a baby will remain safe [34–36]. Many factors, including prematurity or the presence of hemolysis, may interact with the total bilirubin to precipitate or prevent the development of kernicterus. The unbound bilirubin fraction, i.e. the fraction which is not bound to serum albumin, has a greater propensity for traversing the blood-brain barrier and entering the basal nuclei than that which is attached to bilirubin. Thus, the unbound fraction may predict subsequent bilirubin-induced neurologic dysfunction, bilirubin encephalopathy or kernicterus to a greater extent than the total bilirubin value [37]. Unfortunately, unbound bilirubin determination is not available as a clinical tool, and, for practical purposes, we have to rely on the total serum bilirubin both to monitor babies for hyperbilirubinemia and for therapeutic decision-making. Unbound bilirubin values may be used in the future to determine the risk of an individual baby developing kernicterus and to decide on therapeutic procedures. Of practical implication, suggesting the need for cautious evaluation of hyperbilirubinemic neonates who have undergone abdominal surgery, may be the recent finding of hypoaalbuminemia associated with increased unbound bilirubin, the latter both individually and relative to total serum bilirubin, in neonates who had undergone abdominal surgery compared with controls in whom surgery had not been performed [38].

Some Specific Conditions with a High Propensity for Kernicterus

Hemolytic versus Nonhemolytic Conditions

Neonates with hemolytic disease or a hemolytic process may be at higher risk of developing bilirubin encephalopathy or kernicterus than those without an obvious hemolytic condition, as reviewed [39, 40]. Whereas an STB concentration of 342–410 μmol/l (20–24 mg/dl) may be associated with kernicterus in a neonate with Rh iso-
immunization, in the absence of a hemolytic condition, an otherwise healthy term infant will rarely be endangered by TSB concentrations in this range.

Few studies actually offer data supportive of this concept. In a study by Ozmert et al. [41], a positive DAT, used as a presumed marker of hemolysis, was associated with lower IQ scores and a higher incidence of neurologic abnormalities than in controls without a positive test. Similarly, Nilsen et al. [42] found that in DAT-positive Norwegian males who had neonatal hyperbilirubinemia for longer than 5 days, IQ scores were significantly lower than average for the general population. In the Jaundice and Infant Feeding Study, Newman et al. [43] evaluated newborns whose STB was \( \geq 428 \, \mu\text{mol/l} \) (25 mg/dl) at the 5-year follow-up. The subgroup which coexperienced hyperbilirubinemia and positive DAT had significantly lower IQ scores than did hyperbilirubinemic counterparts, but with negative DAT. Kuzniewicz and Newman [44] recently reanalyzed data from the Collaborative Perinatal Project, performed between 1959 and 1966, to evaluate possible interaction between a positive DAT result and bilirubin level on neurodevelopmental outcome. Compared with hyperbilirubinemic [STB \( \geq 428 \, \mu\text{mol/l} \) (25 mg/dl)] newborns with a negative DAT result, those infants who were also DAT-positive had significantly lower full-scale IQ scores.

The exact mechanism of the effect of hemolysis in possibly increasing the risk of bilirubin-induced neurologic dysfunction is unknown. One possibility is that hemolyzing babies may have a higher unbound bilirubin fraction than those not actively hemolyzing, but there is no evidence supportive of this concept. Sudden increases in the STB may preclude a ‘safety mechanism’ whereby bilirubin is distributed within the body’s tissues. Resultant high STB concentrations may predispose to bilirubin crossing the blood-brain barrier.

Hemolysis should not be regarded as a prerequisite for developing bilirubin encephalopathy. Babies without obvious hemolysis, but who did develop kernicterus have been reported [12]. The Crigler-Najjar syndrome, associated with hyperbilirubinemia but not with increased hemolysis, may frequently be complicated by bilirubin encephalopathy [45].

**Specific Hemolytic Conditions**

Both immune and nonimmune hemolytic conditions contribute to a large extent to series of infants with extreme hyperbilirubinemia or bilirubin encephalopathy [15, 25–27]. While nowadays Rh disease is seldom encountered in most Westernized countries, this situation is not necessarily so in developing countries. In India, Pakistan and Nigeria, for example, the majority of women do not receive anti-D prophylaxis and it is estimated that thousands of women will develop anti-RhD antibodies annually [46]. Approximately half the babies born to these women will develop Rh hemolytic disease, and Zip-pursky and Paul [46] estimate that as many as 100,000 children may be born annually with RhD hemolytic disease in developing countries.

Currently, the most common etiologic condition resulting in hyperbilirubinemia due to immune hemolysis is DAT-positive ABO heterospecificity. Anti-C, anti-E and other isoimmunizations, while rare, may result in severe hyperbilirubinemia and kernicterus. On the non-immune front, G-6-PD deficiency continues to play an important part in the pathophysiology of kernicterus, with hereditary spherocytosis and pyruvate kinase deficiency occurring less frequently.

G-6-PD deficiency warrants special mention [9, 10]. The condition is transmitted via the X chromosome, and as a result males are more frequently affected than females. Affected newborns develop hyperbilirubinemia to a greater extent than G-6-PD-adequate controls. This hyperbilirubinemia may be attributed to a combination of moderately increased hemolysis in combination with a predilection for diminished bilirubin conjugation [47, 48], the latter due to presence of a (TA) \( p \) polymorphism \((UGT1A1*28)\) in the promoter of the A1 exon encoding the UDP-glucuronosyltransferase \((UGT1A1)\) bilirubin-conjugating enzyme [49]. Occasionally a severe episode of hemolysis may result in large amounts of bilirubin being produced, which may overcome even the most efficient bilirubin-conjugating systems. Exponential increases in the STB may follow with the tragic complication of kernicterus in its wake. As already noted, G-6-PD deficiency is overrepresented, compared with the background population, in series of infants with extreme hyperbilirubinemia or kernicterus [15, 25, 26]. Neonatal screening for G-6-PD deficiency is available [50]. While precautionary measures will not prevent acute hemolytic attacks in all infants, the knowledge that their infant is G-6-PD-deficient should increase parental awareness of the dangers of the condition and facilitate early approach to medical facilities to obtain treatment.

**Nonhemolytic Conditions**

**Late Preterm Infants**

A major nonhemolytic risk factor exacerbating severe neonatal hyperbilirubinemia with the potential for developing kernicterus is that of late preterm gestation (new-
borns born between 34 and 36 completed weeks) [51, 52]. Activity of the bilirubin-conjugating enzyme UGT 1A1 is more immature than in the term infant and as a result bilirubin conjugation may be diminished. The prevalence, severity and duration of neonatal jaundice in late preterm infants may be exacerbated when coexistent with breastfeeding, male sex, G-6-PD deficiency or other i terogenic factors. While many of these infants are cared for in a regular well-baby nursery, they should be treated with great caution and not as if they were regular babies. In-hospital screening for jaundice, adequate parental education and meticulous postdischarge follow-up are necessary to detect those in the process of developing hyperbilirubinemia so as to institute treatment prior to the serum bilirubin reaching dangerous levels.

Very Low Birth Weight Premature Infants

Despite the high frequency of some degree of clinical jaundice in very low birth weight (VLBW) newborns, autopsy findings of kernicterus in these infants at low peak concentrations of STB (low bilirubin kernicterus) [53, 54], and the common notion that VLBW premature infants are at high risk for bilirubin-related neurologic damage, bilirubin-attributable neurodevelopmental abnormalities have not consistently been noted in long-term follow-up studies [55, 56]. Nevertheless, although specific guidelines have yet to be universally agreed to and a wide range of indications exists, management guidelines for the treatment of hyperbilirubinemia in small preterm infants do differ from those for term infants and include commencement of phototherapy and performance of exchange transfusion at lower levels of STB than in term counterparts, as reviewed [56, 57].

A dearth of kernicterus, even among cases in whom serum bilirubin levels were allowed to exceed recommended values for performing exchange transfusion, noted in postmortem series of premature infants published in the latter quarter of the last century led some to feel that low bilirubin kernicterus was no longer a major problem in this neonatal group [58, 59]. However, several reports from diverse countries including Germany [60], Holland [61] and Japan [62–64] comprising at least 10 VLBW infants, all <28 weeks’ gestation with moderate hyperbilirubinemia in whom the maximal STB concentration did not exceed 272 μmol/l (15.9 mg/dl) and who developed kernicterus, have recently been published and summarized by Moll et al. [60]. It is of note that neurologic features characteristic of classical ABE were not cardinal features of these infants’ clinical courses during the neonatal period. Moll et al. [60] responded to this possible ‘resurgence’ of low bilirubin kernicterus by lowering the bilirubin thresholds for phototherapy in their nursery for very sick infants with birth weight <1,000 g who had additional risk factors including anemia, sepsis or intraventricular hemorrhage. However, because of the inability to relate specific peak STB concentrations to developmental outcome or pathological kernicterus, combined with the rarity of kernicterus in general, it remains to be seen whether this change of strategy will be successful.

Since the turn of the millennium, several countries have responded to the continuation of appearance of cases of kernicterus by either formulating guidelines for the management of hyperbilirubinemia or modifying preexisting guidelines. The most comprehensive of these, and perhaps the most internationally used, are those of the Subcommittee on Hyperbilirubinemia of the American Academy of Pediatrics published in 2004 with an additional commentary in 2009 [5, 67]. National guidelines have also been published in Canada, the UK, South Africa, Israel and Norway [68–72]. The basic principles of hyperbilirubinemia management include the seeking out and recognition of risk factors with the potential of increasing the development of hyperbilirubinemia or exacerbating bilirubin encephalopathy, vigilant in-hospital and postdischarge clinical monitoring for jaundice, adequate breastfeeding support, and assessment that newborns are being properly hydrated and fed. Indications

Kernicterus Is Still with Us: What Can We Do to Prevent It?

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for phototherapy and/or exchange transfusion should be formulated taking into account the dynamic changes in serum bilirubin during the first days of life, risk factors potentiating hyperbilirubinemia and gestational age. Because of early discharge, the peak in serum bilirubin frequently occurs when the infant is already at home, and of paramount importance is the concept that each and every newborn should be assessed for unexpected jaundice by a health authority within a few days of discharge. Any serum or transcutaneous bilirubin value should be plotted on the hour of life specific bilirubin nomogram and assessed along with the risk of subsequent hyperbilirubinemia, according to the percentile for the specific hour of life at which the blood was drawn [73]. More recent recommendations include universal predischarge bilirubin screening of all infants, either by serum sampling or using noninvasive transcutaneous techniques to assess the risk of subsequent hyperbilirubinemia, and planning follow-up [67].

As already noted, neurologic signs attributable to ABE may be transient provided the infants are treated rapidly and effectively with prompt lowering of the STB. Some newborns may be saved the tragic outcome by early, aggressive and effective treatment. Clinical presence of neurologic signs attributable to hyperbilirubinemia should not be interpreted as a reason to withhold treatment [5]. Extreme hyperbilirubinemia in any newborn should be treated as an acute medical emergency by preparing for exchange transfusion as soon as possible while providing intense phototherapy in the interim in a hospital with facilities for performing exchange transfusion if necessary. The infants should be treated by a ‘crash-cart’ approach [74].

Conclusions

Despite major efforts to increase awareness of the condition and formulate guidelines for prevention and treatment, severe neonatal hyperbilirubinemia with the devastating potential, albeit rare, of bilirubin encephalopathy and/or kernicterus continues to plague us into the third millennium. Many cases may be preventable, but because of some conditions associated with sudden, unpredictable and extreme hemolytic crises, it is unlikely that kernicterus will ever be completely eliminated. Abiding by formal guidelines for the detection and treatment of severe hyperbilirubinemia and relating to extreme hyperbilirubinemia as an acute medical emergency will hopefully decrease the incidence of the condition. In developing countries, large sums of money will have to be invested in order to revamp existing medical services and focus on the needs of newborn babies [75].

Disclosure Statement

The authors have no conflicts of interest to declare with regard to any of the material included in the manuscript.

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